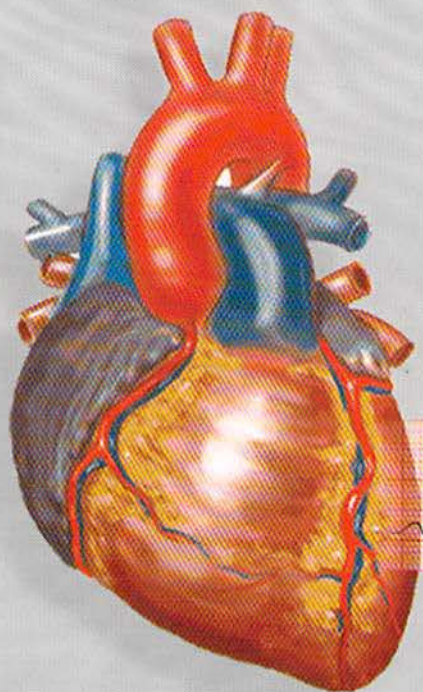


Human

PHYSIOLOGY

For medical students



CIRCULATION



**CARDIOVASCULAR SYSTEM
(CVS)**

MAGDI SABRY, MD

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**HUMAN
PHYSIOLOGY
FOR MEDICAL STUDENTS**

CARDIOVASCULAR SYSTEM

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2011

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DEDICATED TO

***MY TEACHERS THROUGHOUT MY LIFE, particularly the
first 2 teachers, my late parents.***

***MY FAITHFUL LATE WIFE, the light that disappeared
from life but is everlasting inside me.***

***MY SONS, SHERIF, AMR AND ESSAM, AND THEIR WIVES,
their love gives me hope and interest in life and makes their
happiness my chief goal.***

***MY GRANDCHILDREN, AHMED, NOURHAN and SAMA
SHERIF, YASMIN and MOHAMMED AMR, AND AYA and ALY ESSAM,
the beautiful young angels that have added a new kind of
happiness to my life.***

PREFACE

With recent advances in the field of human physiology, it has become urgent to provide an up to date review on the subject.

This book is provided to help medical students in understanding modern cardiovascular physiology. It presents the whole subject in a brief, comprehensive, and up to date form.

Great effort was done to perfect such a vast subject in an easily understandable expression and in a such reasonable bulk. It includes as much simplified and clear illustrations as possible, and to maintain simplicity, they have been presented in a diagrammatic form, photographs were greatly excluded.

The major part of my gratitude should be given to all who taught me as well as to my family who, patiently, supported me during preparation of this book.

Any suggestions, remarks or criticism will be greatly welcomed, heartily appreciated and very much considered.

I hope this book will be a real help to undergraduate medical students as well as to postgraduates and candidates of higher degrees, in the field of human physiology.

MAGDI SABRY, 1993

Second edition 1998

Third edition 2003

Preface to the fourth edition

This new edition is original both in shape and contents. Unproved data and material that is no longer relevant were eliminated and all chapters have been extensively revised and updated. More figures and illustrations were introduced, and recent data were added elsewhere specially about the cardiovascular regulatory mechanics and the circulation through special regions, and most subjects have been completely rewritten.

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CHAPTER 1

MECHANISM OF HEART BEATING

The *cardiovascular system (CVS)* is a closed system in which blood circulates, and it consists of the **heart and blood vessels** (figure 1).

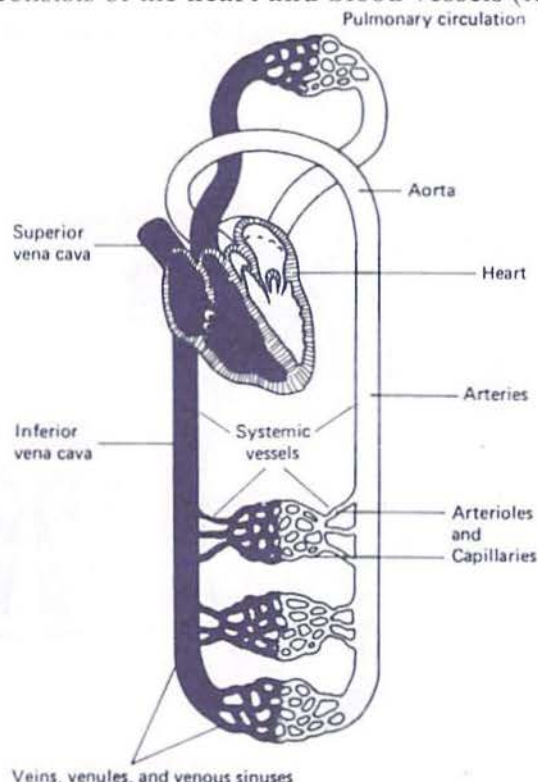


Figure 1 : The cardiovascular system.

Functional anatomy of the heart

The human heart is a muscular organ enclosed in a thin fibrous connective tissue sac called the **pericardium**. This sac contains a few ml of a clear watery fluid which serves as a lubricant to heart movement. It is also relatively inelastic (which limits excessive enlargement of the heart). The wall of the heart is formed of a special kind of muscle fibres called the **cardiac muscle fibres**, and they are collectively known as the **myocardium**. The arteries that supply the myocardium are branches from the aorta and are called the **coronary arteries**. The inner surface of the myocardium is lined by a thin layer of endothelial cells called the **endocardium**. This endothelial cell layer does not only line the heart cavities but also the entire vascular system. The heart is divided into **right and left halves** each of which consists of one atrium and one ventricle, and the 2 atria are separated by an **inter-atrial septum** while the 2 ventricles are separated by an **interventricular**

septum. The *atrial myocardium is much thinner* than that of the ventricles, and the *left ventricular wall is about 3 times as thick as the right ventricular wall* (about 15 and 5 mm respectively).

THE HEART (CARDIAC) VALVES : Each ventricle has an **inlet** (= **atrioventricular**) valve which separates it from the atrium), and an **outlet valve** which separates it from the vessel that originates from it (figure 2 left).

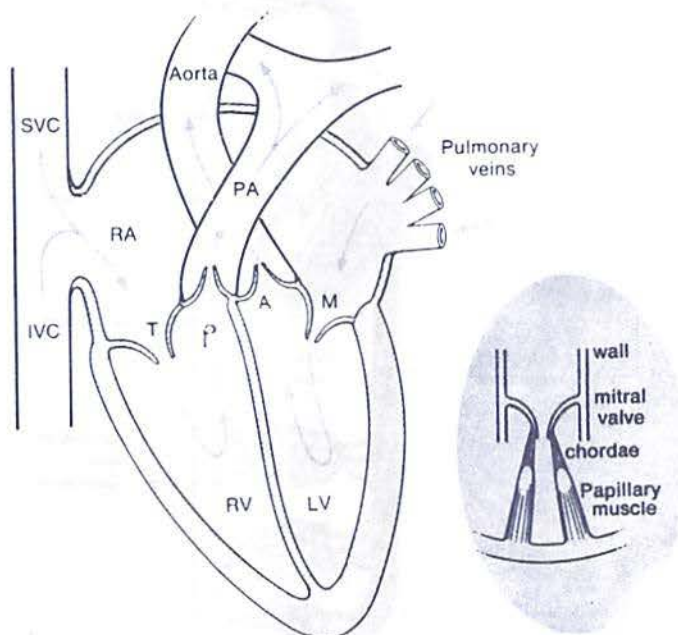


Figure 2 : Direction of blood flow in the heart (left) and the papillary muscles (right). T and M = Tricuspid and Mitral valves. A and P = Aortic and Pulmonary valves. PA = Pulmonary Artery. SVC = Superior vena cava and IVC = Inferior vena cava.

The flow of blood through both the heart and the vascular system is *uni-directional* (i.e. it flows in one direction only) *from the atria to the ventricles to the arteries then to the veins and finally to the atria again*. *Such unidirectional blood flow is produced by the action of 4 valves in the heart that open and close passively i.e. only as a result of pressure differences across them* (see the cardiac cycle, chapter 3). These valves include the following :

(A) The atrioventricular valves (= A-V valves) : These constitute the inlet valves to the ventricles (see above), and they include **(1) The tricuspid valve in the right side :** This consists of 3 cusps (or leaflets) and it allows blood flow only from the right atrium to the right ventricle **(2) The bicuspid (or mitral) valve in the left side :** This consists of 2 cusps, and it allows blood flow only from the left atrium to the left ventricle.

****** Certain muscles called the *papillary muscles* project from the ventricular walls into the ventricular cavities. The tendons of these muscles are firm fibrous cords called the *chordae tendineae* and they are attached to the *margins of the cusps of the A-V valves* (figure 2 right). These muscles contract at the same time of ventricular contraction, leading to pull of the chordae tendineae downwards. This *prevents eversion of the cusps of the A-V valves into the corresponding atria during ventricular contraction*.

(B) The semilunar valves : These constitute the **outlet valves** from the ventricles (see above), and they include **(1) The pulmonary valve in the right side :** This allows blood flow *only from the right ventricle to the pulmonary artery* (figure 2 left) **(2) The aortic valve in the left side :** This allows blood flow *only from the left ventricle to the aorta* (figure 2 left). Each of these valves is formed of 3 cusps, which are *half-moon shaped pockets* (so they are frequently also called the *semilunar valves*).

****** The atrial and ventricular musculatures are separated by fibrous tissue that surrounds the atrioventricular valvular openings (= **A-V ring or fibrous skeleton of the heart**). This ring is an **electrical insulator**, so *action potentials cannot normally be conducted from the atria to the ventricles via this tissue* and they are conducted **only via the AV node & AV bundle**(page 6)

DIVISIONS OF THE CIRCULATORY SYSTEM

(1) The systemic (or greater) circulation

This circulation starts from the left ventricle → aorta → large arteries → small arteries → arterioles → capillaries → venules → veins → SVC and IVC (superior and inferior venae cavae) → right atrium.

(2) The pulmonary (or lesser) circulation

This circulation lies in *series* with the systemic circulation, and it starts from the right ventricle → pulmonary trunk (= pulmonary artery) → lungs → pulmonary capillaries → 4 pulmonary veins → left atrium.

(3) The special circulations

These include the circulations at specific sites e.g. the **capillary (= micro)**, **lymph**, **coronary** and **cerebral circulations**.

CHARACTERISTICS OF VARIOUS BLOOD VESSELS

(1) The aorta and pulmonary artery are *elastic vessels*. The aortic elasticity is *essential to maintain the arterial blood pressure* (page 101).

(2) The medium-size and small arteries are *muscular low resistance vessels* that deliver blood to the tissues at a considerable pressure.

(3) The arterioles are *muscular high resistance vessels* that regulate the blood flow to tissues and *maintain the arterial blood pressure* (page 101).

(4) The capillaries are *exchange vessels* through which fluids and various substances are exchanged between the blood and the tissues.

(5) The veins and pulmonary vessels are *capacitance vessels* that accommodate large volumes of blood under low pressure (*volume reservoir*).

****** During rest, *more than half of the blood volume (about 54 %) is present in the systemic veins, in contrast to 12 % in the heart, 11 % in the arterial system, 5 % in the capillaries, and 18 % in the pulmonary vessels.*

THE LOW AND HIGH PRESSURE SYSTEMS

The **left ventricle and the systemic arterial system** (aorta, arteries and arterioles) constitute a *high pressure system* because it normally contains a small percentage of the blood volume but under a high pressure. On the other hand, the **systemic veins, pulmonary vessels and heart chambers other than the left ventricle** constitute a *low pressure system* that normally contains a much greater amount of the blood volume (see above) but under a low pressure.

FUNCTIONS OF THE ATRIA AND VENTRICLES

The pumping action of the ventricles is the main force that propels blood to the peripheral circulatory system, so loss of such function is fatal. On the other hand, the **atria perform the following functions**

- (1) **Blood storage** : They receive and store the venous return during ventricular systole then deliver it to the ventricles during ventricular diastole
- (2) The atrial walls contain *stretch receptors* that monitor changes in the intra-atrial pressure and initiate *several regulatory cardiovascular reflexes*
- (3) Certain atrial cells secrete the *atrial natriuretic peptide (ANP)* which favours excretion of Na^+ and water by the kidney (refer to endocrine glands).

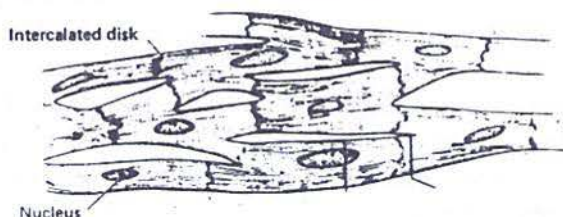


Figure 3 : The contractile cardiac muscle fibres

TYPES OF CARDIAC MUSCLE FIBRES

(A) Contractile cardiac muscle fibres (99 %)

These are the fibres that constitute the *atrial and ventricular walls*. They are characterized by the following :

(1) They branch and interdigitate (figure 3), *but each fibre is a separate cell* surrounded by a cell membrane (the sarcolemma).

(2) They are **striated** like skeletal muscles and also contract by a similar mechanism. They contain *actin, myosin, troponin and tropomyosin*, but the *T system is located at the Z lines* (not at the A-I junctions). They also contain an additional protein called **dystrophin** (the congenital deficiency of which leads to one type of a serious heart disease known as *cardiomyopathy*).

(3) There are **intercalated disks (or discs)** along the muscle fibres (figure 3) which are always present at the Z lines. These disks are actually cell membranes that separate individual fibres from one another. At each disk, the cell membranes fuse and form **gap junctions** that allow free diffusion of ions. Therefore, the disks provide **low-resistance bridges** that allow rapid spread of excitation waves from one fibre to other fibres.

Accordingly, *from the functional point of view*, the cardiac muscle constitutes a **syncytium** that obeys the **all or none law**, and leads to its contraction as one unit (resulting in a more efficient pumping force). The heart contains **2 functional syncytia** (*the walls of the 2 atria form one syncytium and the walls of the 2 ventricles form the other*), and these syncytia are completely separated from each other by the fibrous A-V ring (page 3).

(B) Autorhythmic cardiac muscle fibres (1 %)

These are *modified* almost **non-contractile cardiac muscle fibres** (because they contain few contractile myofibrils) that are specialized for **generation (initiation), conduction and distribution of cardiac impulses** (action potentials) that stimulate the contractile muscle fibres. They constitute a network known as the **conducting system of the heart** (see next), and they contact the contractile muscle fibres via **gap junctions**.

MECHANISM OF HEART BEATING

Heart beating (i.e. *ventricular contraction*) is produced by the effect of action potentials that are initiated & propagated to the ventricles by a **specialized muscular conducting system in the heart**. This consists of **3 parts** :

(A) The nodal system

This includes 2 nodes that are located in the *right atrium* (figure 4) :

(1) **The sinoatrial node (SAN)**, which is located in the wall of the right atrium near the opening of the superior vena cava.

(2) **The atrioventricular node (AVN)**, which is located at the base of the right atrium near the interventricular septum.

(B) The internodal system

This system consists of 3 muscular tracts that connect the SAN to the AVN:

(1) *The anterior internodal tract* : This extends directly from the SAN to the AVN and *also* gives a branch to the left atrium (through the interatrial septum) called *Bachmann's bundle*, which excites the left atrium at nearly the same time of right atrial excitation, *so both atria would contract simultaneously*.

(2) *The middle internodal tract (= Wenckebach's tract)*.

(3) *The posterior internodal tract (= Thorel's tract)*.

(C) The His-Purkinje system

This system transmits the excitation waves to the right and left ventricular muscle, and it includes the following 3 structures :

(1) **The A-V (or atrioventricular) bundle (= bundle of His)** : This consists of a strand of specialized cardiac muscle cells that arise from the A-V node and pass through the A-V fibrous ring to the upper part of the interventricular septum. It is the *only normal muscular connection between the atria and the ventricles, and the AV node and AV bundle normally constitute the only electrical connection that links the atria and the ventricles*. Sometimes, the heart may contain other muscular connections e.g. the *bundle of Kent* (page 65).

(2) **The right and left branches of the bundle of His** : These start at the top of the interventricular septum and run down on either side of this septum under the endocardium to the apex of the heart then they are reflected upwards along the inner sides of the lateral walls of the ventricles to the base of the heart.

(3) **The Purkinje fibres** : These are fine fibres that arise from the right and left bundle branches and transmit excitation waves to the ventricular muscle.

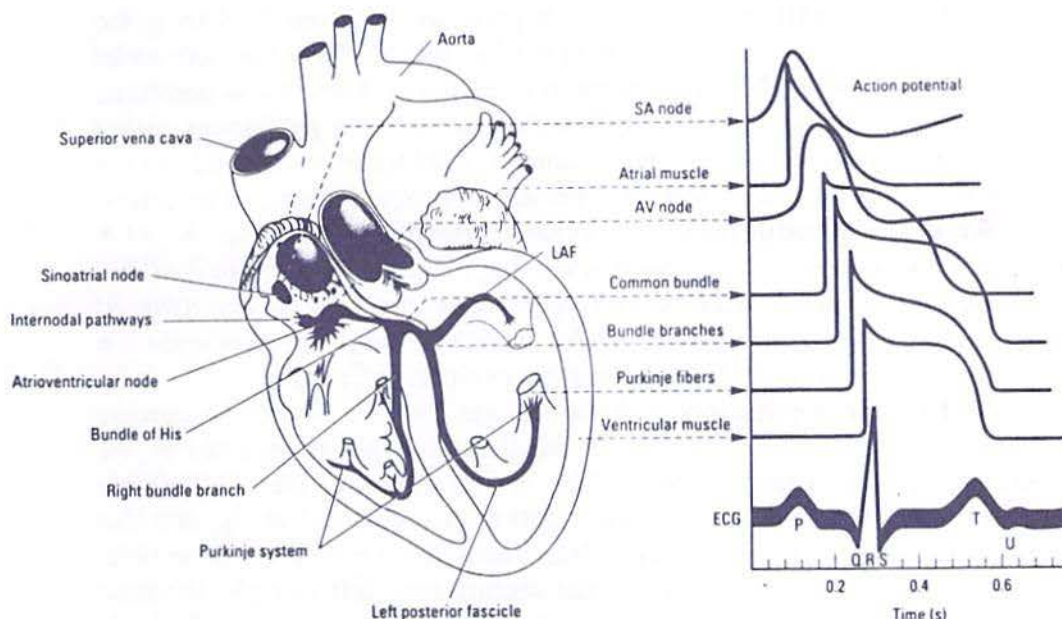


Figure 4 : The conducting system of the heart (left) and the action potentials recorded from various regions of the heart (right)..

INITIATION AND SPREAD OF CARDIAC EXCITATION

- Cardiac excitation is initiated by an action potential (= cardiac impulse) that is spontaneously generated by self-excitable cardiac cells present in the **nodal and His-Purkinje systems** called **autorhythmic cells** (see above). The cells in the various sites of these systems differ in their inherent rates of generating action potentials, but **normally the site that has the fastest rate of autorhythmicity drives the rest of the heart at its rate and is known as the pacemaker (= speed maker) of the heart.**

- Normally, the SAN has the fastest inherent rate of discharge (100-110 /minute) and is thus the **normal (or primary) pacemaker of the heart**. In this case, the **non-SA nodal autorhythmic cells are unable to assume their slower rates of discharge** because they are depolarized by the impulses that originate in the SA node before they reach the threshold of their own rhythms. However, these cells are **latent pacemakers** that can be brought into action **but only after failure of the SA node autorhythmicity due to disease.**

- In the nodal tissues (particularly the SAN), there are special round cells that contain few organelles. These cells are probably the actual pacemaker cells (so they are frequently called the **P cells**).

- **Atrial excitation** : The cardiac impulse spreads from the SAN to the atria leading to their excitation. It then reaches the AVN *via both the atrial musculature and the 3 internodal tracts* (see above). These tracts constitute more rapidly-conducting pathways but they seem to be *functional rather than anatomical* (because the most accurate histological studies did not yet demonstrate clearly the presence of specialized bundles of cells in the atria).

- **AV nodal conduction** : The *cardiac impulse is delayed in the AVN about 0.1 second* (page 20). Such AV delay is important because it *allows complete atrial depolarization and contraction (as well as emptying of their blood content into the ventricles) before ventricular depolarization and contraction occur* (refer to the cardiac cycle, chapter 3).

- **Ventricular excitation** : After leaving the AV node, the cardiac impulse travels rapidly down the AV bundle and is then transmitted by the Purkinje system to the ventricles. The muscle fibres in the His-Purkinje system are specialized for rapid propagation of action potentials, and this results in excitation of every part of both ventricles at nearly the same time. Excitation starts in the interventricular septum from **left to right** (because the *septum receives a twig from the left bundle branch*) then the Purkinje fibres transmit the impulse outwards through the ventricular walls (i.e. from the **endocardium to the epicardium**).

****** The conducting system is more organized, more developed and more complex in the ventricles than in the atria. This is because the ventricular muscle mass is much larger and requires such highly organized conducting system to convey excitation to both ventricles at nearly the same time (so that a single strong contraction that ejects blood efficiently is produced). If ventricular excitation depends only on the syncytial structure of the myocardium (i.e. on cell to cell spread of the cardiac impulse via the gap junctions), the ventricular muscle near the AV node will contract before excitation reaches the heart apex, which would result in an inefficient pumping.

OVERDRIVE SUPPRESSION

This is depression of a pacemaker automaticity after its excitation for a period at a greater frequency than its inherent rhythmicity. This phenomenon explains why automaticity in the latent pacemakers of the heart is depressed by the stronger SAN automaticity. It also explains the *depression of SAN automaticity if an atrial ectopic focus fires at a higher frequency* than that of the SAN e.g. in cases of *atrial flutter and fibrillation* (in which case, the ectopic focus becomes the pacemaker of the heart). In the later condition, if the ectopic focus stops firing suddenly, the SAN will resume its activity but not immediately, because it requires an interval to recover from depression (= **sinus node recovery time**). During this interval, the heart stops beating and if it is prolonged, syncope (= loss of consciousness) may occur.

CHAPTER 2

PROPERTIES OF THE CARDIAC MUSCLE

In addition to the **syncytium** property of the cardiac muscle (= *if one fibre is stimulated, the entire myocardial unit contract*), it also has the properties of (a) **Excitability** (b) **Automaticity and rhythmicity or auto-rhythmicity** (page 16) (c) **Conductivity** (page 19) (d) **Contractility** (page 21).

(A) EXCITABILITY (ELECTRICAL ACTIVITY OF THE HEART)

This is the ability of the cardiac muscle fibres to respond to adequate stimuli, and the response is their depolarization and generation of action potentials.

Myocardial excitation contraction coupling

Depolarization of the cardiac muscle fibres markedly increases their cytosolic (intracellular) Ca^{2+} content, which combines to troponin C leading to their contraction *exactly as occurs in skeletal muscles*, and their relaxation also occurs as in skeletal muscles (refer to nerve and muscle).

During cardiac excitation, the cytosolic Ca^{2+} is derived from 2 sources (1) The sarcoplasmic reticulum (*the main source*) (2) The extracellular fluid (the depolarization wave causes opening of the **slow (= long-lasting) Ca^{2+} channels in the sarcolemma**, leading to Ca^{2+} influx from the ECF into the cardiac muscle fibres *mainly during the plateau phase of the action potential* (page 11).

Although the amount of Ca^{2+} diffusing from the ECF is normally very small, yet it is very important because *it acts as a signal for release of much more Ca^{2+} from the sarcoplasmic reticulum*.

The *force of contraction is directly proportional to the amount of cytosolic Ca^{2+}* (therefore, the drugs that block the Ca^{2+} channels decrease Ca^{2+} influx, leading to disappearance of the plateau phase of the cardiac action potential and weakening of the force of cardiac muscle contraction).

Relaxation of the cardiac muscle occurs as a result of decreasing the intracellular Ca^{2+} content to its pre-contraction level (so that its content *remains constant*). This occurs by (a) Active reuptake of Ca^{2+} into the sarcoplasmic reticulum (b) Active pumping of excess Ca^{2+} outside the cardiac muscle fibres by an *antiport $\text{Na}^+ - \text{Ca}^{2+}$ exchanger carrier*.

THE CARDIAC ACTION POTENTIALS

Normally, **slow and fast response cardiac action potentials** are recorded (figure 5). The former is recorded from the *S-A node and A-V node* because they are poor in gap junctions (so the cardiac fibres in these nodes are called *slow-response fibres*) while the latter is recorded from the *atria and ventricles as well as the His - Purkinje system* which are rich in gap junctions (so the cardiac fibres in these regions are called *fast-response fibres*).

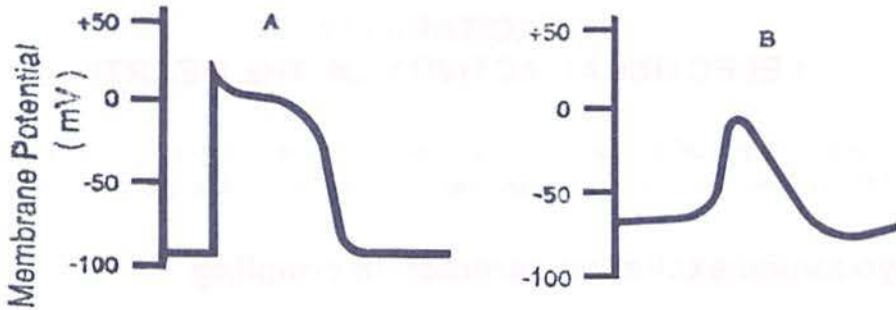


Figure 5 : A fast response action potential (A) and a slow response action potential (B) recorded from a ventricular muscle and the SAN respectively.

Characteristics of the cardiac action potentials

Figure 5 A shows a fast-response action potential recorded from a *ventricular muscle fibre* (those recorded from the *atrial and Purkinje fibres* vary in the duration of their components, and are shown in figure 4). The resting potential in these fibres is about **-90 mV**, and the action potential is characterized by (1) A steep upstroke (2) A large amplitude (up to +20 to +30 mV) (3) Presence of a **plateau**.

On the other hand, figure 5 B illustrates a slow response action potential recorded from the SA node. The resting potential in the fibres of this region is less negative than in the fast response fibres (**-55 to -60 mV**), and the action potential is characterized by (1) Presence of a **prepotential** (page 17) (2) A less steep (i.e. slow) upstroke (3) A small amplitude (up to +1 to +10 mV) (4) No (or a brief) **plateau**.

Ionic basis of the cardiac action potential

(1) The fast response action potential consists of 5 phases (figure 6). These phases and the associated ionic changes include the following :

(a) Phase 0 (upstroke) : This is caused by rapid depolarization of the cell membrane (which overshoots to +20 to +30 mV). It is due to rapid Na^+ influx secondary to activation (opening) of voltage-gated fast Na^+ channels.

(b) Phase 1 (early or partial repolarization) : This is caused by (1) Inactivation (closure) of Na^+ channels (2) Little K^+ efflux (as a result of a small increase in K^+ permeability secondary to opening of some K^+ channels).

(c) Phase 2 (plateau) : This is a *unique* phase in the fast response action potential and is caused by increased Ca^{2+} influx secondary to opening of *slow L (= long-lasting) Ca^{2+} channels* (this is the Ca^{2+} that stimulates Ca^{2+} release from the sarcoplasmic reticulum during excitation contraction coupling, page 9). Ca^{2+} influx balances the increasing K^+ efflux, so the membrane potential is kept constant as a plateau close to 0 mV (figure 6).

(d) Phase 3 (rapid repolarization) : This is caused by a marked increase in K^+ efflux in addition to inactivation (= closure) of the Ca^{2+} channels.

(e) Phase 4 (restoration of the resting membrane potential) : This is achieved by the *Na^+-K^+ pump* which pumps outwards the Na^+ that had entered the cardiac muscle fibre during phase 0, and pumps inwards the K^+ that had left the cardiac muscle fibre during phases 1, 2 and 3 (see above).

(2) The slow response action potential can also be divided into 5 phases (figure 6). However, the upstroke is *slow* and is preceded by a *prepotential* (page 17), reaches only to +1 to +10 mV and is caused mainly by *an increase in Ca^{2+} influx via slow L Ca^{2+} channels*. There is almost *no plateau*, and phases 1, 2 and 3 merge together constituting a descending repolarization phase which is *more gradual* than in the fast response action potential (figure 9), but is also caused by an increase in K^+ efflux.

The following table summarizes the differences between the fast and slow response action potentials (in a ventricular and SAN fibres respectively).

Fast response action potential	Slow response action potential
The resting potential is about -90 mV and remains constant till excitation	The resting potential is -55 to -60 mV and is unstable (showing prepotential)
The upstroke is rapid. It is due to Na^+ influx, and reaches up to +20 to +30 mV	The upstroke is slow. It is due to Ca^{2+} influx, and reaches only to +1 to +10 mV
There is a prominent plateau	There is no (or a brief) plateau
The falling phase is rapid	The falling phase is gradual

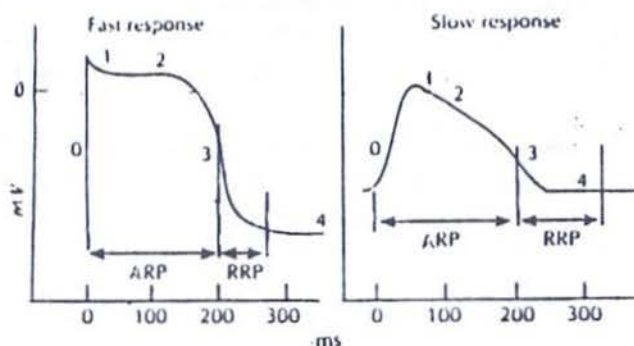


Figure 6 : Excitability changes during the fast and slow response cardiac action potentials.

Excitability changes during cardiac action potentials

During the fast and slow action potentials, the corresponding cardiac muscle fibres pass in the following **2 stages of refractoriness** (= *unresponsiveness*) which occur mainly as a result of inactivation of the Na^+ channels in the cardiac muscle fibres (figure 6) :

(1) Absolute refractory period (ARP) : This is a period during which the excitability level is **zero** (i.e. no stimulus whatever its strength can initiate a propagated action potential). In case of the fast response, it extends from the *start of phase 0 to the middle of phase 3*, while in the slow response, it continues *till very late in phase 3*. During the ARP, strong stimuli were found to produce a local response which has a low amplitude and conducts slowly, so this period is also called the *effective refractory period (ERP)*.

(2) Relative refractory period (RRP) : This is a period during which the excitability is improved but still below normal, and only stimuli that exceed the normal threshold can produce propagated action potentials (which are slow-rising and of low amplitudes). In case of the fast response, it occupies the remainder of phase 3, while in the slow response, it **extends in phase 4** after repolarization of the muscle fibre is completed. The later property of the slow response fibres is called *post-repolarization refractoriness*.

****** A third phase of excitability called the **supernormal phase** occurs only in the *fast response fibres*. This phase **occupies phase 4** of the action potential, and during it the excitability is more than normal (so weak stimuli can produce propagated action potentials). Early in this phase, an excitation wave from an ectopic focus (or any other external source) is dangerous because it may lead to ventricular fibrillation under certain conditions, so this period has been called the **vulnerable period** (page 62).

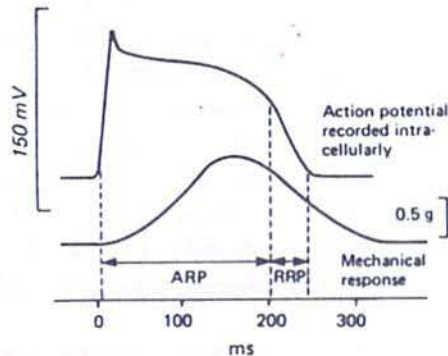


Figure 7 : Time relationship between the mechanical response, the action potential and the various phases of excitability in a ventricular muscle fibre.

Time relationship between electrical and mechanical responses

In the contractile fast response fibres, the mechanical response starts just after the depolarization phase (phase 0) of the action potential. It continues for a longer time than the action potential (figure 7), and the systole reaches maximum at the end of the plateau phase (phase 2) while the first half of the diastole coincides with the rapid phase of repolarization (phase 3) and the second half of diastole coincides with phase 4.

Characteristics and importance of the ARP in cardiac muscle

Compared with skeletal muscles, the duration of the ARP in the contractile (= fast response) cardiac muscle fibres is much longer. This is due to presence of the *plateau phase of the action potential* (during which the membrane potential is zero i.e. the cell membranes are depolarized). It occupies phases 0, 1, 2 and the first half of phase 3, and is almost **as long as the period of contraction**. Accordingly, the cardiac muscle *cannot be re-stimulated during contraction*. This is an **important protection mechanism**

that prevents summation of contractions and tetanus (= sustained contraction) of the cardiac muscle, which is **fatal** because the pumping function of the heart will be lost (such function requires alternate periods of contraction and relaxation, to eject blood then fill again respectively).

The duration of the cardiac ARP is determined mainly by the duration of the plateau phase of the action potential. The following factors affect the duration of the ARP *through affecting the duration of the plateau* :

(1) **Regional factors** : The ARP is longer in the ventricles than in the atria because the plateau is longer in the ventricular muscle (figure 4).

(2) **Autonomic innervation** : Sympathetic stimulation increases the membrane conductance to Ca^{2+} , leading to prolongation of both the plateau phase of the action potential as well as the ARP. By an opposite mechanism, parasympathetic (vagal) stimulation shortens the atrial ARP.

(3) **Chemical factors** : Hypocalcemia, O_2 lack (= hypoxia) and certain drugs (e.g. procainamide and quinidine) prolong the ARP.

FACTORS THAT AFFECT CARDIAC EXCITABILITY

(1) **Nervous factors** : Sympathetic stimulation increases the excitability and may activate ectopic foci leading to tachycardia or extrasystoles (see below)

(2) **Physical factors** : An increase in the body temperature increases the cardiac excitability and vice versa.

(3) **Chemical factors** :

(a) **Inorganic ions** :

- **Calcium** : Hypercalcemia decreases the myocardial excitability and shortens the ARP while hypocalcemia exerts opposite effects.

- **Potassium** : Hyperkalemia decreases the myocardial excitability and may cause cardiac arrest in diastole while hypokalemia increases it and may activate ectopic foci.

- **Sodium** : Changes in the serum Na^+ level do not significantly affect the myocardial excitability but they affect the amplitude of the action potential.

(b) **Hypoxia and ischemia** : These decrease the myocardial excitability.

(c) **Hormones** : Catecholamines and thyroxine increase the myocardial excitability and may activate ectopic foci (like sympathetic stimulation).

(d) **Drugs** : Xanthines (e.g. caffeine and theophylline) increase the myocardial excitability while cholinergic drugs, quinidine and procainamide decrease it (*the latter 2 drugs are used to depress active ectopic foci*).

EXTRASYSTOLES (= PREMATURE BEATS)

These are abnormal systoles (contractions) that are produced by impulses discharged from a *hyperexcitable ectopic focus* (= a focus other than the S-A node). These foci may arise in the ventricle (producing *ventricular extrasystoles*) or in the atria or the A-V node (producing *supraventricular extrasystoles*), and they may develop normally (e.g. as a result of *excessive smoking*) or pathologically (e.g. in *myocardial ischemia*).

Mechanism of extrasystoles & the compensatory pause

Extrasystoles are produced **only when an ectopic focus discharges during diastole i.e. during the RRP** (impulses discharged during systole fall in the ARP and are not effective). They are called **premature beats** because they do not increase the heart rate, and they lead to *irregularity of the heart rate and are frequently associated with pulse deficit* (page 41) because they are usually weak and cause ejection of small amounts of blood.

Ventricular extrasystoles are followed by long intervals called **compensatory pauses (CPs)** which *replace some missed normal beats*, so the *duration of an extrasystole and the following compensatory pause + the preceding contraction = duration of 2 normal beats* (figure 8).

The **cause of the CP** is that *the normal impulse discharged from the S-A node after an extrasystole reaches the ventricle while it is in the contraction phase (i.e. the ARP) of the extrasystole, so it will be ineffective and accordingly no contraction occurs and a CP will be recorded instead*. However, the next SA node impulse will be effective (because the ventricle will be no longer in the refractory state) and will produce a contraction which is usually *stronger than normal* (= **post-extrasystolic potentiation**, page 24). Such strong contraction + increased ventricular filling with blood during the CP *increase the stroke volume and the amplitude of the arterial pulse*.

Atrial extrasystoles are often followed by short or incomplete (or no) CPs because the impulses that produce them *also stimulate the S-A node*, which causes rapid-shift to the normal sinus rhythm.

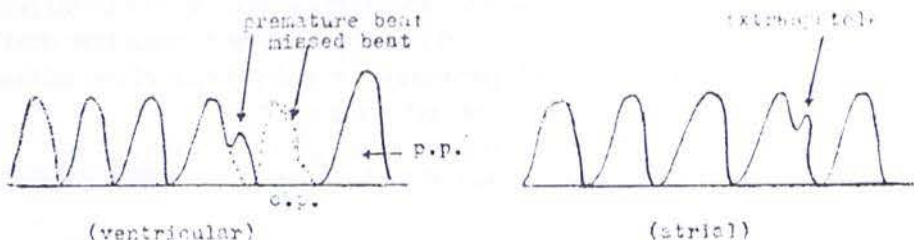


Figure 8 : Extrasystoles (premature beats). CP = Compensatory Pause.
P.P. = Post-extrasystolic Potentiation.

Physiological differences between cardiac and skeletal muscles

(1) Skeletal muscle contraction is initiated by impulses reaching the motor end plates via the motor nerves while cardiac muscle contraction depends on impulses initiated in a *pacemaker and transmitted directly from cell to cell*.

(2) The resting membrane potential of the slow response cardiac muscle fibres (in the nodal tissue) only is unstable leading to **prepotentials** and spontaneous discharge (see next page).

(3) The action potential in the contractile (fast response) cardiac muscle fibres only shows a **plateau** so the *ARP is much longer* than in skeletal muscle.

(4) Skeletal muscle *only* can be *tetani*zed due to summation of contractions.

(5) In the *cardiac muscle* only, the excitation-contraction coupling depends on the **extracellular Ca^{2+}** .

(6) The cardiac muscle only obeys the *all or none law*.

(B) AUTOMATICITY & RHYTHMICITY(AUTORHYTHMICITY)

Automaticity is the property of *self-excitation* (i.e. ability of spontaneous generation of action potentials independent of extrinsic stimuli). On the other hand, rhythmicity is the *regular generation* of these action potentials.

The contractile cardiac muscle fibres do not normally generate action potentials. In contrast, all parts of the conducting system are normally capable of autorhythmicity, but the *normal (primary) pacemaker is the S-A node*, while the *A-V node is a secondary pacemaker* and the *Purkinje system is a tertiary pacemaker*. The latter 2 act as **latent pacemakers** i.e. the A-V node acts only if the S-A node is damaged, while the tertiary pacemaker takes over only if impulse conduction via the A-V node is completely blocked.

The normal inherent rate of autorhythmicity of the S-A node (= **sinus rhythm**) is 100-110 / minute, while that of the A-V node (= **nodal rhythm**) is 45-60 / minute and that of the Purkinje system (= **idioventricular rhythm**) is 25-40 / minute. The unequal autorhythmic activity in various regions is due to differences in their rates of developing prepotentials (see next)

Autorhythmicity is a **myogenic property** (i.e. independent of the cardiac nerve supply). This is evidenced by the following :

(1) Completely denervated hearts continue beating rhythmically.

(2) Hearts removed from the body and placed in suitable solutions continue beating for relatively long periods.

(3) The transplanted hearts have no nerve supply but they beat regularly.

****** The effect of various factors on autorhythmicity is called **chronotropism**. Factors that increase autorhythmicity are called + ve chronotropic factors while factors that decrease it are called - ve chronotropic factors.

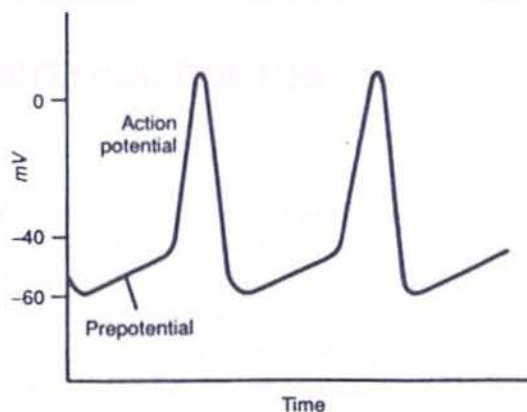


Figure 9 : SA node potentials (prepotential and action potential).

MECHANISM OF AUTORHYTHMICITY

The prepotential (or pacemaker potential)

The pacemaker cells in the nodal tissue (SA node and AV node) have a resting membrane potential of -55 to -60 mV. However, it is **not stable**, so that after each impulse, gradual depolarization occurs spontaneously till a threshold (the firing level) is reached (-40 to -45 mV) at which an action potential (i.e. an impulse) is initiated (figure 9). This gradual depolarization is called **pacemaker potential**, **prepotential** or **diastolic depolarization**.

Mechanism of the pacemaker potential

The pacemaker potential (or prepotential) occurs mainly secondary to a *progressive spontaneous reduction of the cell membrane permeability to K^+* (which decreases K^+ efflux, thus the membrane will be depolarized). Ca^{2+} influx via *T (transient) fast Ca^{2+} channels* also contribute.

****** A drug that opens the K^+ channels *decreases both the rate of firing of the SA node and the heart rate* because (1) It increases the cell membrane permeability to K^+ , and this opposes the spontaneous reduction of the cell membrane permeability to K^+ that produces the pacemaker potential (see above) (2) It promotes K^+ efflux and hyperpolarization of the S-A node membrane, and this prolongs the time required to reach the firing threshold.

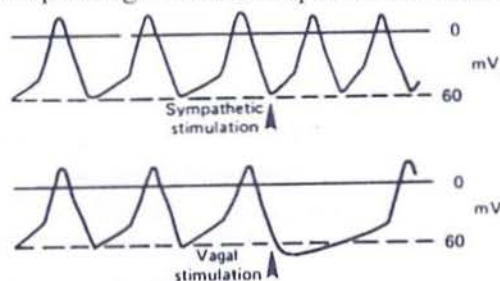


Figure 10 : Effects of sympathetic and parasympathetic (vagal) stimulation on the slope of prepotential in the SA node..

FACTORS THAT AFFECT AUTORHYTHMICITY

(1) NERVOUS FACTORS

(a) Parasympathetic stimulation decreases (slows) the slope of the prepotentials (figure 10), and accordingly the autorhythmicity of the pacemaker cells is reduced resulting in *bradycardia*. Such *-ve chronotropic effect* occurs secondary to *opening of the K^+ channels* (by the action of the released acetylcholine on M_2 muscarinic receptors) which leads to the same effects produced by the drugs that open the K^+ channels (see above).

(b) Sympathetic stimulation increases (accelerates) the slope of the prepotentials (figure 10), and accordingly the autorhythmicity of the pacemaker cells is increased resulting in *tachycardia*. Such *+ve chronotropic effect* occurs secondary to *closure of the K^+ channels* (by the action of the released norepinephrine on β_2 receptors) which leads to more rapid development of the prepotentials.

(2) PHYSICAL FACTORS

Autorhythmicity is affected by temperature. A rise of the body temperature (e.g. in muscular exercise and fevers) increases the heart rate by about 10-20 beats / minute for each 1°C rise. On the other hand, in cases of hypothermia the autorhythmicity and heart rate are decreased. These effects occur secondary to changes in the metabolic activity of the pacemaker cells in the SAN.

(3) MECHANICAL FACTORS

Distention of the right atrium increases the autorhythmicity of the pacemaker SAN probably secondary to stretch (= **Bainbridge effect**, page 73). This response is important in transplanted hearts (which are denervated) to increase their rates of beating when the venous return increases.

(4) CHEMICAL FACTORS

(a) **Hormones** : Catecholamines and thyroxine increase the autorhythmicity by a mechanism similar to that of sympathetic stimulation (see above).

(b) **Blood gases** : Mild hypoxia increases the autorhythmicity (by stimulating the pacemaker cells both directly and by increasing sympathetic activity) while severe hypoxia & hypercapnia inhibit it and may cause cardiac arrest.

(c) **Inorganic ions** : Hyperkalemia and hypercalcemia decrease the slope of the pacemaker potential and inhibit the autorhythmicity, while hypokalemia and hypocalcemia increase it (by affecting K^+ fluxes). On the other hand, both hypernatremia and hyponatremia tend to inhibit autorhythmicity.

(d) **H^+ ion concentration (pH)** : Acidosis decreases while alkalosis increases the autorhythmicity (but in severe alkalosis, it is also inhibited).

(e) **Drugs** : Sympathomimetic drugs increase the autorhythmicity while cholinergic drugs inhibit it. Digitalis, although increasing the cardiac contractility, depresses the nodal tissue activity and exerts vagal-like effects specially on the A-V node (reducing its rhythmicity and conductivity).

(f) **Toxins** : Certain toxins inhibit the autorhythmicity e.g. the toxin released by the bacteria that cause diphtheria (in this disease, a high fever associated with bradycardia indicates cardiac depression).

(C) CONDUCTIVITY

This is the ability of the cardiac muscle to transmit action potentials from one fibre to the adjacent fibre. The impulses originating in the S-A node are conducted to the atria then through the conducting system to the ventricles (page 8), and the *last activated parts are the posterobasal portion of the left ventricle and the pulmonary conus of the right ventricle*.

The conduction velocity varies in different regions of the heart as follows :

- (1) It is *lowest in the nodal tissues* because they are poor in gap junctions (*about 0.05 meter / second in the A-V node and even less in the S-A node*).
- (2) It is *moderate* in atrial and ventricular muscle (average 1 meter / second)
- (3) It is *highest in the Purkinje network* because it is rich in gap junctions (*about 4 meters / second*). This allows complete and simultaneous excitation of both ventricles.

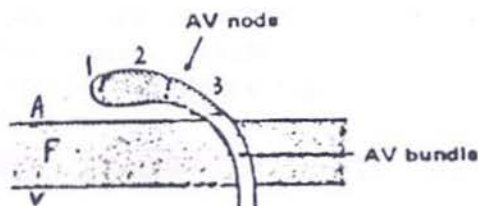


Figure 11 : The A-V nodal region. 1 = AN region. 2 = N region. 3 = NH region. A = atrium. V = ventricle. F = fibrous tissue septum.

CONDUCTION IN THE A-V NODAL REGION

The A-V node can be functionally divided into 3 regions (figure 11) :

- (a) **The AN (= Atrio-Nodal) region** : This is the upper part. It constitutes a transitional zone between the atrial muscle and the next region of the node.
- (b) **The N (=Nodal) region** : This is the middle and main part of the node.
- (c) **The NH (= Nodal-His) region** : This is the lower part. Its fibres merge with the fibres that constitute the bundle of His.

A-V nodal conduction is *characterized by a delay of about 0.1 second for impulse transmission to the ventricles* due to 2 main factors :

(1) The nodal muscle fibres are slowly-conducting (slow-response fibres) that are small in size and poor in gap junctions.

(2) The **special characteristics (properties) of the N region of the A-V node**, which include the following :

(a) The *conduction velocity is slowest in the N region* (but however, the **greatest A-V nodal delay occurs in the AN region of the node** because its path length is greater than that of the N region)..

(b) The conduction of impulses through both the AN and NH regions is all or none while it is **decremental in the N region** (i.e. the amplitude of the action potential decreases gradually as it traverses the N region).

(c) The fibres in the N region show **post-repolarization refractoriness** i.e. they remain relatively refractory (= inexcitable or unresponsive) for a significant time (phase 4) after their complete repolarization (page 12).

Importance of A-V nodal delay

(1) It allows *the atria to depolarize, contract and empty their blood content into the ventricles before ventricular excitation occurs*.

(2) It limits conduction of impulses through the A-V node (**which cannot normally conduct more than 220 or 230 impulses / minute**) in cases of high atrial rhythms e.g. atrial fibrillation and flutter (page 61). This function is important because excessive ventricular tachycardia is associated with marked shortening of the diastolic periods (during which ventricular filling occurs) which results in pumping less amounts of blood than normal.

FACTORS THAT AFFECT CARDIAC CONDUCTIVITY

(1) NERVOUS FACTORS

Sympathetic stimulation accelerates conductivity (so it reduces the A-V nodal delay) while vagal stimulation delays it and may cause heart block.

(2) PHYSICAL FACTORS

Rise of the body temperature increases the rate of cardiac conductivity while it is decreased in cases of hypothermia.

(3) CHEMICAL FACTORS

(a) **Hormones** : Conductivity is increased by catecholamines & thyroxine.

(b) **Blood gases** : Conductivity is decreased in cases of O_2 lack (ischemia).

(c) **Inorganic ions** : Conductivity is decreased in most cases of electrolyte disturbance (specially K^+).

(d) **H^+ ion concentration (pH)** : Conductivity is decreased in acidosis and slightly increased in alkalosis.

(e) **Drugs** : Conductivity is decreased by digitalis & cholinergic drugs (specially at the A-V node), while it is increased by sympathomimetic drugs.

****** The conductivity is also increased in the Wolff-Parkinson-White syndrome (page 65) and decreased in cases of heart block (page 65).

(D) CONTRACTILITY (CARDIAC MECHANICS)

The property of contractility does not simply mean the ability of the cardiac muscle fibres to contract but it refers to the *force generated by myocardial contraction*.

The mechanism of myocardial muscle contraction is the *same as that occurring in skeletal muscles*. It also depends on availability of Ca^{2+} and the process of *excitation-contraction coupling* was explained before (page 9)

FACTORS THAT AFFECT CARDIAC CONTRACTILITY

These include the cardiac preload and afterload, in addition to intrinsic (cardiac) factors and extrinsic (extracardiac) factors.

(A) CARDIAC PRELOAD (*length-tension relationship*)

What is meant by the preload ? : The preload is the *load that determines the resting length of a muscle before contraction*.

Cause of cardiac preload : The *amount (or rate) of venous blood return is the main determinant of the cardiac preload*, and since the venous return also determines the end diastolic volume (EDV) and pressure (EDP), estimation of either can be used to indicate the magnitude of the cardiac preload.

Effects of cardiac preload : An increase in the cardiac preload increases the *tension developed by the ventricular muscle as well as its velocity of shortening* (see below), resulting in a more forceful ventricular contraction

and an increase in the stroke volume. However, this occurs only up to a certain limit (at a sarcomere length of 2.2 microns) after which the peak ventricular performance is decreased (figure 12).

Such effects are due to an increase in (a) The extent of overlap between actin and myosin (which increases the number of interacting cross bridges) (b) The affinity of the contractile protein troponin C to Ca^{2+} .

Starling (or Frank-Starling) law

This law describes the above **length-tension relationship** in muscles. It states that " *Within limits, the force of myocardial contraction is directly proportional to the initial length of the cardiac muscle fibres* ".

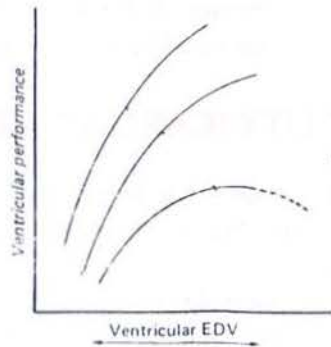


Figure 12 : The Frank-Starling curves.

The Frank- Starling curves

These curves illustrate the Starling law in various conditions of myocardial contractility (figure 12). The middle curve shows the relation between the EDV and the level of ventricular performance in normal resting conditions, while the upper curve shows the effect of positive inotropic factors and the lower curve shows the effect of negative inotropic factors.

Significance of Starling law

Starling law autoregulates the cardiac function according to changes in the initial length of the cardiac muscle fibres as follows :

(1) **In normal hearts :** It allows changes in the right ventricular output to match changes in the venous return (VR), and it also maintains equal outputs from both ventricles e.g. if the systemic (VR) increases, the right ventricular EDV and output also increase, which matches the increased (VR). At the same time, the pulmonary (VR) will also increase leading to increase of the left ventricular EDV and output, which balances the right ventricular output.

(2) **In failing hearts** : In this condition, the ventricular pumping power is decreased. This leads to rise of the EDV, which increases the myocardial contractility (thus preventing much decrease in the cardiac output).

(3) **In denervated hearts (e.g. transplanted hearts)** : In these hearts, autoregulation of myocardial contractility through Starling law becomes the main mechanism that adjusts the pumping capacity of the heart.

(4) **In cases of hypertension** : In these cases, the stroke volume of the left ventricle would decrease. However, the remaining blood volume in the left ventricle + blood returning from the left atrium during diastole will increase its EDV. This leads to a powerful left ventricular contraction according to Starling law, thus the accumulated blood in the left ventricle will be pumped in spite of the increased arterial blood pressure.

(B) CARDIAC AFTERLOAD (force-velocity relationship)

What is meant by afterload ? : The afterload is the *load that the muscle faces when it begins to contract*.

Cause of cardiac afterload : The cardiac afterload is determined by the magnitude of *aortic impedance* (resistance against which the left ventricle ejects blood). The latter is determined by the level of the aortic pressure and other factors (e.g. it increases in aortic valve stenosis and in polycythemia).

Effects of cardiac afterload : Changes in the afterload affect the extent and velocity of shortening of the cardiac muscle as shown in the **force-velocity curve** (figure 13). The *velocity of shortening is inversely proportional to the magnitude of afterload*. At zero afterload, maximal velocity is achieved (V_{max}) while at a certain afterload (L_0 in the lower curve in figure 13), the velocity becomes zero and the muscle contracts isometrically.

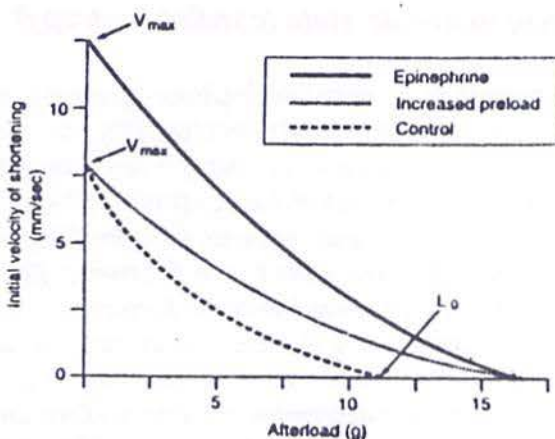


Figure 13 : The force-velocity curve in the cardiac muscle.

****** The velocity of shortening is also affected by changes in the *preload and the contractility state*. An increase in the preload increases the initial velocity of shortening at any given afterload but not the V_{max} (middle curve in figure 13). On the other hand, +ve inotropic agents (as epinephrine) increase both the initial & maximal velocity of shortening (upper curve in figure 13).

(C) INTRINSIC (CARDIAC) FACTORS

A significant loss of the ventricular muscle mass (e.g. due to infarction) decreases the myocardial contractility proportionately. However, apart from this factor, 2 other cardiac factors affect myocardial contractility. These are :

(1) The heart rate (Force-frequency relationship)

An increase in the frequency of cardiac stimulation (e.g. in cases of tachycardia) increases the contractility (a *staircase phenomenon*), and vice versa. This is due to the increase in the number of depolarizations (which increases the intracellular Ca^{2+} content and its availability to the contractile proteins).

Also, the beats that follow the compensatory pauses of premature beats (= extrasystoles) are usually stronger than normal. This is called **postextrasystolic potentiation** (page 15), and is due to *more release of Ca^{2+} from the sarcoplasmic reticulum (SR)* which occurs as follows : The premature impulse increases the intracellular Ca^{2+} content as a result of Ca^{2+} influx from the ECF, so the amount of Ca^{2+} reuptake by the (SR) is increased during the compensatory pause, and accordingly the next impulse leads to release of excess Ca^{2+} from the (SR) which increases the force of contraction.

(2) The cardiac inotropic state (cardiac inotropy)

Cardiac inotropy is a peculiar intrinsic property of the cardiac muscle. It signifies that the myocardial contractility can be increased or decreased *independent of changes in the preload or afterload*. It is determined primarily by the amount of (or sensitivity to) the delivered Ca^{2+} to the contractile proteins (actin and myosin), and *the factors that increase the myocardial contractility are called +ve inotropic factors while the factors that decrease it are called -ve inotropic factors*.

The cardiac inotropic state is increased in cases of tachycardia (see above) and *is also influenced by many extracardiac factors {see below}*.

****** *The major factors that determine cardiac performance include (1) The preload (2) The after load (3) The frequency of heart contraction (4) The cardiac inotropic state.*

(D) EXTRINSIC (EXTRACARDIAC) FACTORS

These factors affect the *cardiac inotropic state*, and they include :

(1) NERVOUS FACTORS

Sympathetic stimulation exerts a +ve inotropic effect by increasing (a) The heart rate (b) Cyclic-AMP in the cardiac muscle fibres (which leads to activation of the Ca^{2+} channels resulting in more Ca^{2+} influx from the ECF and more Ca^{2+} release from the sarcoplasmic reticulum). Conversely, parasympathetic (vagal) stimulation exerts a -ve inotropic effect by opposite mechanisms, but on **the atrial muscle only** because the vagi nerves do not supply the ventricles (refer to autonomic N.S.).

(2) PHYSICAL FACTORS

A moderate rise of the body temperature increases cardiac contractility (by increasing the Ca^{2+} influx and ATP formation in the cardiac muscle) while an excessive rise of the body temperature (e.g. in fevers) exhausts the metabolic substrates in the cardiac muscle and decreases its contractility. Hypothermia also decreases cardiac contractility.

(3) CHEMICAL FACTORS

(A) Hormones : *Catecholamines* (= epinephrine, norepinephrine and dopamine) and the pancreatic hormone *glucagon* exert a +ve inotropic effect by increasing the cyclic-AMP content. *Insulin and thyroxine* also exert a +ve inotropic effect (the former by enhancing glucose transport into the cells and the latter by enhancing the response to catecholamines and formation of enzymes that have a high ATPase activity).

(B) Blood gases : Moderate hypoxia (= O_2 lack) and hypercapnia (= CO_2 excess) increase the cardiac contractility through stimulating the *peripheral chemoreceptors* (which increases the sympathetic discharge to the heart). On the other hand, severe hypoxia and hypercapnia *directly depress the cardiac muscle and decrease its contractility*.

(C) H^+ ion concentration (pH) : An increase of the blood $[\text{H}^+]$ i.e. drop of the blood pH (acidosis) produces a -ve inotropic effect by inhibiting Ca^{2+} release from the (SR) and its binding to troponin C, and may stop the heart in

diastole (like excess K^+). On the other hand, a decrease of the blood $[H^+]$ i.e. rise of the blood pH (alkalosis) produces a + ve inotropic effect by an opposite mechanism, and may stop the heart in systole (like excess Ca^{2+}).

(D) Inorganic ions :

- **Sodium** : Hypernatremia favours Na^+ influx & Ca^{2+} efflux (by the antiport Na^+ - Ca^{2+} exchanger carrier), so it exerts a - ve inotropic effect. On the other hand, hyponatremia exerts a +ve inotropic effect by an opposite mechanism.
- **Potassium** : Hyperkalemia exerts a - ve inotropic effect and *may stop the heart in diastole* because the excess K^+ in the ECF causes partial depolarization of the cardiac muscle cells, so the amplitude of the action potential is decreased leading to less Ca^{2+} influx. On the other hand, hypokalemia produces a + ve inotropic effect by an opposite mechanism.
- **Calcium** : Hypercalcemia exerts a + ve inotropic effect as a result of more Ca^{2+} influx. It prolongs the systole on the expense of the diastole and the heart *may stop in systole* (**Ca^{2+} rigor**), so *i.v. Ca^{2+} injections should be given very slowly*. On the other hand, hypocalcemia usually has a little (or no) -ve inotropic effect, since lowering of the serum Ca^{2+} level causes fatal tetany before affecting the heart (refer to endocrine glands).

(E) Toxins : Certain snake venoms and the toxin released by the bacteria that cause diphtheria produce a - *ve inotropic effect* (mostly by a direct action on the contractile mechanism of the cardiac muscle)

(F) Drugs :

- **Cardiac glycosides (e.g. digitalis)** : These drugs inhibit the Na^+ - K^+ ATPase in the cell membranes, so the intracellular Na^+ concentration increases. However, the Na^+ - Ca^{2+} antiport carrier promotes Na^+ efflux in exchange with Ca^{2+} influx from the ECF. Accordingly, the intracellular Ca^{2+} concentration increases, producing a + *ve inotropic effect*.
- **Xanthines (e.g. caffeine and theophylline)** : These drugs exert a +*ve inotropic effect* through increasing the intracellular cyclic-AMP (by inhibiting the phosphodiesterase enzyme which breaks down cyclic-AMP).
- **Quinidine, barbiturates, procainamide** (and other anesthetic drugs) as well as the **Ca^{2+} channel blocker drugs** all exert a - *ve inotropic effect* by decreasing the Ca^{2+} influx into the cardiac muscle fibres.

CHAPTER 3

THE CARDIAC CYCLE

Acting as a **hydraulic pump**, the human heart has periods of contraction (during which blood is pumped into the large arteries) that alternate with periods of relaxation (during which blood fills the heart). These contraction and relaxation periods occur in cycles known as the **cardiac cycles**, each of which consists of a period of contraction called **systole** followed by a period of relaxation called **diastole**, and they normally occur at a rate of about **75 cycles per minute during rest** (i.e. each cycle lasts about **0.8 second**).

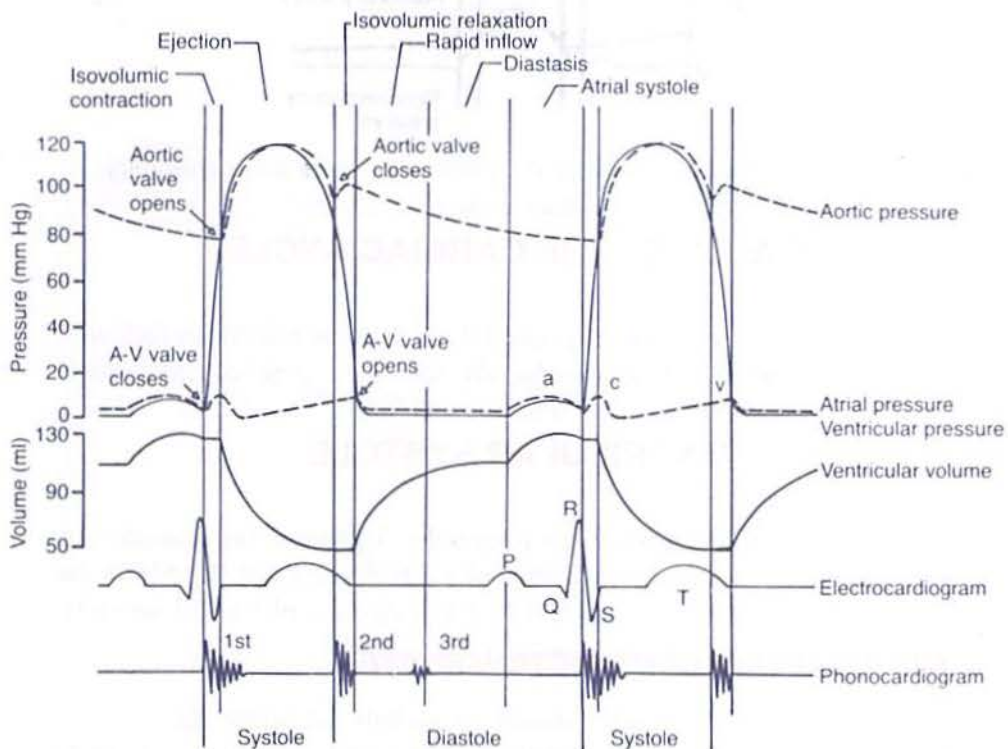


Figure 14 : Phases and events that occur in the left side of the heart and aorta during the cardiac cycle.

The mechanical events (i.e. *changes in pressure and volume*) that occur in the **left side of the heart** during one cardiac cycle as well as the *aortic pressure changes* and the associated *valvular events, heart sounds and ECG tracing* are all shown in figure 14.

The mechanical events that occur in the right side of the heart and the pulmonary artery **are similar to those occurring in the left side and aorta** (figure 15), *except that the right ventricular pressure during systole and the pressures in the pulmonary artery are much lower than those in the left ventricle and aorta* (so constituting part of the **low pressure system**, page 4)

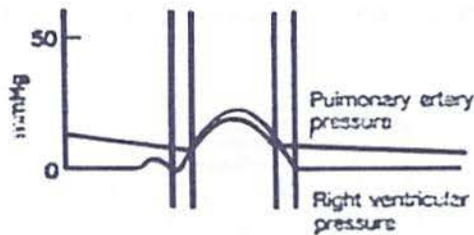


Figure 15 : Changes that occur in the right ventricular and pulmonary arterial pressures during the cardiac cycle.

PHASES OF THE CARDIAC CYCLE

The cardiac cycle starts by *atrial systole* (about 0.1 second) that is followed by *ventricular systole then ventricular diastole*. The *atrial diastole* starts early in ventricular systole then continues for about 0.7 second.

VENTRICULAR SYSTOLE

This lasts about **0.3 second** and it includes **3 phases** (a) *Isometric (= isovolumetric or isovolumic) contraction* phase (0.05 second) (b) *Maximum (rapid) ejection* phase (0.15 second) (c) *Reduced ejection* phase (0.1 second).

(a) THE ISOMETRIC CONTRACTION PHASE

The events that occur during this phase include the following :

- (1) **Ventricular pressure and volume :** The ventricles contract isometrically (i.e. without shortening of the cardiac muscle fibres) thus the *ventricular pressure rises sharply while the ventricular volume remains constant*.
- (2) **Valves :** Both *A-V valves are closed* because the ventricular pressures exceed the atrial pressures, and both *semilunar valves also remain closed*.
- (3) **Sounds :** The *first heart sound* is produced in this phase as a result of closure of the A-V valves (see below).

(4) **Atrial pressure** : This increases slightly on closure of the A-V valves due to ballooning (bulging) of their cusps into the atrial cavities.

(5) **Aortic and pulmonary artery pressures** : These gradually decrease due to flow of blood from the aorta and pulmonary artery to the peripheral smaller vessels. They decrease to minimum values at the end of this phase (= **diastolic blood pressure**) just before ventricular ejection (to about 80 mmHg in the aorta and 9 mmHg in the pulmonary artery) .

(6) **ECG** : The Q wave starts about 0.02 second before this phase, while the R and S waves are recorded during it.

(b) THE MAXIMUM EJECTION PHASE

The events that occur during this phase include the following :

(1) **Ventricular volume and pressure** : The ventricles contract isototonically (i.e. the cardiac muscle fibres are shortened), thus the ventricular volumes rapidly decrease while the ventricular pressures increase gradually to a maximum of 120 mmHg in the left ventricle and 25 mmHg in the right ventricle.

(2) **Valves** : Both AV valves remain closed while both *semilunar valves open* when the ventricular pressures exceed the diastolic pressures in the great arteries (about 80 mmHg in the aorta and 9 mmHg in the pulmonary artery) which results in blood ejection in these vessels.

(3) **Aortic and pulmonary artery pressures** : These increase gradually (due to blood ejection from the ventricles) to a maximum that nearly equals the maximum pressures in the corresponding ventricles i.e. 120 mmHg in the aorta and 25 mmHg in the pulmonary artery (= **systolic blood pressure**).

(4) **Atrial pressure**: This is initially decreased due to widening of the atrial cavities which occurs as a result of (a) Atrial diastole (b) Pulling of the A-V fibrous ring downwards during ventricular contraction (c) Descent of the cusps of the AV valves after blood ejection from the ventricles. *The atrial pressure then gradually increases due to the continuous venous return.*

(5) **Sounds** : The first heart sound continues for a brief period in this phase

(6) **ECG**: The S-T segment is recorded and the T wave starts in this phase.

(c) THE REDUCED EJECTION PHASE

The events in this phase are just continuation of those occurring in the preceding phase, and they include the following :

(1) **Ventricular volume** : This is further decreased.

(2) **Ventricular pressure** : This starts to decrease due to pumping of most of the ventricular blood into the great arteries during maximum ejection.

(3) **Aortic and pulmonary artery pressures** : These decrease because the ejected amounts of blood from the ventricles into the aorta and pulmonary artery become smaller than the amount of blood leaving them to the

peripheral smaller vessels. However, they gradually become slightly more than the ventricular pressures (although both are decreasing), but in spite of that the blood flow from the ventricles to the aorta and pulmonary artery continues by the **momentum of the forward blood flow**.

(4) **Valves** : The semilunar valves are open and the AV valves remain closed

(5) **Atrial pressure** : This is still increasing due to continuous venous return

(6) **Sounds** : There are no sounds in this phase.

(7) **ECG**: The ascending limb & top of the T wave are recorded in this phase

PROTODIASTOLE

This is a very short period that *was described* between the end of ventricular systole and start of ventricular diastole. However, this period is generally considered a part of the isovolumetric relaxation phase.

VENTRICULAR DIASTOLE

This lasts about **0.5 second** and it includes **4 phases** :

(1) **Isometric (= isovolumetric or isovolumic) relaxation phase** (0.05 sec.)

(2) **Rapid (maximal) filling phase (Early ventricular diastole)** (0.15 sec.).

(3) **Slow (reduced) filling phase (Mid-ventricular diastole)** (0.20 sec.).

(4) **Late ventricular diastole** (coincident with atrial systole). (0.10 sec.).

(a) ISOMETRIC (ISOVOLUMETRIC) RELAXATION PHASE

The events that occur during this phase include the following :

(1) **Ventricular pressure and volume** : The ventricles relax isometrically (without lengthening of the cardiac fibres) so the ventricular pressure falls sharply to about 0 mmHg while the *ventricular volume remains constant*.

(2) **Atrial pressure** : This is still increasing due to continuous venous return

(3) **Valves** : *Both semilunar valves are closed* because the arterial pressures exceed the ventricular pressures, and both *A-V valves also remain closed*.

(4) **Sounds** : The *second heart sound* is produced in this phase as a result of closure of the semilunar valves (see below).

(5) **ECG** : The descending limb of the T wave is recorded in this phase.

(6) **Aortic and pulmonary artery pressures** : These gradually decrease (due to flow of blood from the aorta and pulmonary artery to the peripheral smaller vessels) with appearance of a **dicrotic notch** and a **dicrotic wave** (see next).

THE DICROTIC NOTCH and WAVE (WINDKESSEL EFFECT)

At the start of isometric relaxation, the blood in the aorta and pulmonary artery flows back towards the corresponding ventricles (because of the higher pressures in these vessels as described above). This results in (a) Closure of the semilunar valves and production of the **second heart sound** (b) A small oscillation (disturbance) on the downslope of the aortic and pulmonary arterial pressure curves called the **dicrotic notch or incisura** (due to vibrations in the blood when the semilunar valves are suddenly closed).

Following the dicrotic notch, a wave called the **dicrotic wave** is recorded due to a slight increase in the aortic and pulmonary arterial pressures (which then decrease gradually due to flow of blood to the peripheral smaller vessels). This wave occupies the diastolic period and is produced as a result of **elastic recoil of the aortic and pulmonary arterial walls**. The latter effect is produced by a mechanism called the **windkessel effect**, which occurs as follows : Stretching of the aorta and pulmonary artery during the ejection phases creates potential energy in their walls, and during isometric relaxation, this energy is converted into kinetic energy which causes these vessels to rebound (leading to their recoil). The windkessel effect maintains forward movement of blood during ventricular diastoles, which renders the **blood flow to the tissues to be continuous** (during both systoles and diastoles) and **not pulsatile** (i.e. not intermittent during systoles only).

(b) RAPID (MAXIMAL) FILLING PHASE

In this phase, the atrial pressure exceeds the ventricular pressure, so the AV valves open and the accumulated blood into the atria rushes into the ventricles. The events that occur include the following :

- (1) **Valves** : The A V valves open while the semilunar valves remain closed
- (2) **Atrial pressure** : This initially decreases due to rush of blood from the atria into the ventricles then it increases due to the continuous venous return.
- (3) **Ventricular pressure** : This initially decreases due to ventricular relaxation by the rushing blood from the atria, then it increases gradually with the increased amount of blood pumped from the atria.
- (4) **Ventricular volume** : This increases markedly as a result of filling of the ventricles by the blood coming from the atria.
- (5) **Aortic and pulmonary artery pressures** : These decrease gradually due to the continuous blood flow from the aorta and pulmonary arteries to the peripheral small arteries.
- (6) **Sounds** : The **3rd heart sound** is produced in this phase (see below).
- (7) **ECG** : The early part of the T-P segment and the U wave (if present) are recorded in this phase.

(c) SLOW (REDUCED) FILLING PHASE (DIASTASIS)

This phase is a continuation of the rapid filling phase and is associated with the following events :

- (1) **Valves** : The AV valves are open while the semilunar valves are closed.
- (2) **Atrial pressure** : This is still increasing due to the venous return.
- (3) **Ventricular pressure and volume** : These gradually increase but at a slower rate (due to reduction of the amount of blood coming from the atria).
- (4) **Aortic and pulmonary artery pressures** : These are still decreasing due to continuous blood flow from the aorta and pulmonary artery to the peripheral small arteries.
- (5) **Sounds** : There are *no sounds* in this phase.
- (6) **ECG** : The late part of the T-P segment and the start of the P wave are recorded in this phase.

DIASTASIS and ATRIAL SYSTOLE

The *slow filling phase* is frequently called **diastasis** because of the very slow filling to the extent that the blood almost stagnates in the heart till the next cycle starts. However, *very late in ventricular diastole*, the atria contract and such **atrial systole** usually causes an additional 20 % filling of the ventricles. The *events that occur during atrial systole include the following*

- (1) **Atrial pressure** : This initially increases due to decrease of the atrial volume, then it decreases due to rush of blood into the ventricles..
- (2) **Ventricular volume and pressure** : These also slightly increase by effect of the blood pumped from the atria.
- (3) **Valves** : The AV valves are open while the semilunar valves are closed.
- (4) **Aortic and pulmonary artery pressures** : These are gradually decreasing due to continuous blood flow from the aorta and pulmonary artery to the peripheral small arteries.
- (5) **Sounds** : The *fourth heart sound* is produced in this phase (see below)
- (6) **ECG** : The P wave starts about 0.02 second before this phase, while the main part of the P wave, the P-R segment and the Q wave occur during it.

REMEMBER

****** The systolic pressure in each *ventricle* is nearly equal to that in its corresponding artery i.e. about 120 mmHg in the left ventricle (as in the aorta) and 25 mmHg in the right ventricle (as in the pulmonary artery). Conversely, the diastolic pressure in each ventricles is equal (about 0 mmHg).

**** The elasticity (compliance) of the aorta is important because (1)** It prevents excessive increase in the systolic pressure during ventricular systole **(2)** It allows continuous blood flow to the tissues (windkessel effect). Thus, in arteriosclerosis, the systolic pressure rises markedly (figure 19) and the blood flow to the tissues becomes almost only during systoles.

**** The AV valves open during atrial systole and the filling phases, and close in the other phases. On the other hand, the semilunar valves open during the ejection phases and close in the other phases.**

**** During the isovolumetric phases (1)** All valves are closed and the ventricles become closed chambers **(2)** The *muscle tension only is changed* (not the muscle length). The tension increases during isovolumetric contraction (= interval between the start of ventricular systole and opening of the semilunar valves), and decreases during isovolumetric relaxation (= interval between closure of the semilunar valves and opening of the AV valves)

**** The amount of blood present in the ventricles just before the start of systole is called the end diastolic volume** (about 130 ml during rest) while the amount of blood that remains in the ventricles after ejection is called the **end systolic volume** (about 50 ml during rest). The ejected amount of blood per beat is therefore about 80 ml and is called the **stroke volume**. It constitutes about 65 % of the end diastolic volume, and this is called the **ejection fraction** (page 77).

**** The incisura (= dirotic notch) that is recorded on the downslope of the arterial pressure curve (figure 14) indicates the end of ventricular systole, closure of the semilunar valves and start of ventricular diastole.**

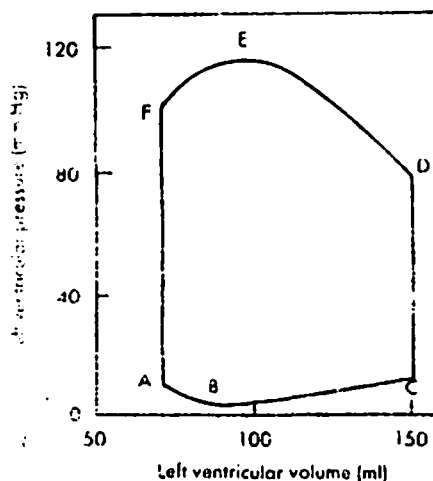


Figure 16 : The left ventricular pressure-volume loop during a cardiac cycle.

The ventricular pressure volume loop during the cardiac cycle

The ventricular pressure and volume changes during the cardiac cycle can be demonstrated in the form of a loop. A normal *left ventricular loop* is shown in figure 16, and is interpreted as follows :

(1) The mitral valve opens at A, and ventricular filling occurs between A and C. The initial decrease in pressure (from A to B) is due to ventricular relaxation by the rushing blood from the left atrium.

(2) The mitral valve closes at C and isometric ventricular contraction occurs between C and D.

(3) The aortic valve opens at D, and rapid ejection occurs between D and E while reduced ejection occurs between E and F.

(4) The aortic valve closes at F, and isometric ventricular relaxation occurs between F and A. At A the mitral valve opens starting a new cycle.

EVALUATION OF LEFT VENTRICULAR PERFORMANCE

This can be carried out by determination of the following periods :

(1) **The total electromechanical systole (QS₂)** : This is the period from the onset of the QRS complex of the ECG to the closure of the aortic valve as determined by the onset of the second heart sound (S₂).

(2) **The left ventricular ejection time (LVET)** : This is the period from the beginning of rise of the arterial pressure to the dicrotic notch.

(3) **The pre-ejection period (PEP)** : This is the difference between QS₂ and LVET. It represents the time for the electrical and mechanical events that precede systolic ejection. The ratio (PEP / LVET') is normally about 0.35, and it increases without changes in QS₂ if the left ventricular performance is decreased.

THE HEART SOUNDS

The heart sounds can be recorded through a sensitive microphone placed on the chest wall (a process called **phonocardiography**). The recorded tracing



Figure 17 : A normal phonocardiogram.

is called the **phonocardiogram**, and it shows that 4 sounds occur normally during each cardiac cycle (figure 17). The first and second sounds are always heard through **auscultation** (= listening by a **stethoscope**). On the other hand, the third sound is sometimes heard in children while the fourth sound is normally inaudible in all ages.

The **first sound occurs at the start of ventricular systole** and is heard as "lub" while the **second sound occurs at the start of ventricular diastole** and is heard as "dup". Since the duration of systole is shorter than that of the diastole (about 0.3 and 0.5 second respectively), heart beating has the rhythm of *lub dup -pause- lub dup -pause- lub dup -pause-*, and so on. In tachycardia, the diastolic periods are reduced, so the pauses are shortened and the identification of the 2 sounds becomes difficult. However, they can still be differentiated by simultaneous palpation of the carotid pulse (the sound that occurs about the same time of that pulse is the first heart sound).

THE FIRST HEART SOUND

Timing in the cardiac cycle : This sound coincides with the onset of ventricular systole, so it falls mainly during the *isometric contraction phase* and also extends in the early part of the *maximum ejection phase* (figure 14).

Cause : Closure of the AV valves

Mechanism : The sound is produced by the vibrations set up in the blood, chordae tendineae and ventricular wall after closure of the AV valves. It is *not the result of snapping shut of the valves* (because blood greatly damps the effect of slapping of the valve leaflets together).

Characters : It is a soft low pitched sound.

Duration : About 0.15 second.

Site of bearing : Closure of the mitral valve is best heard over the apex of the heart at the 5th left intercostal space 10 cm from the midline just internal to the midclavicular line. On the other hand, closure of the tricuspid valve is best heard at the lower end of the sternum (figure 18).

Splitting of the first heart sound

Normally, the *mitral valve closes before the tricuspid valve*, and this would produce splitting of the first sound. However, this is difficult to detect by auscultation (and even by phonocardiography) because the sounds produced by closure of both valves are low pitched and merge into each other.

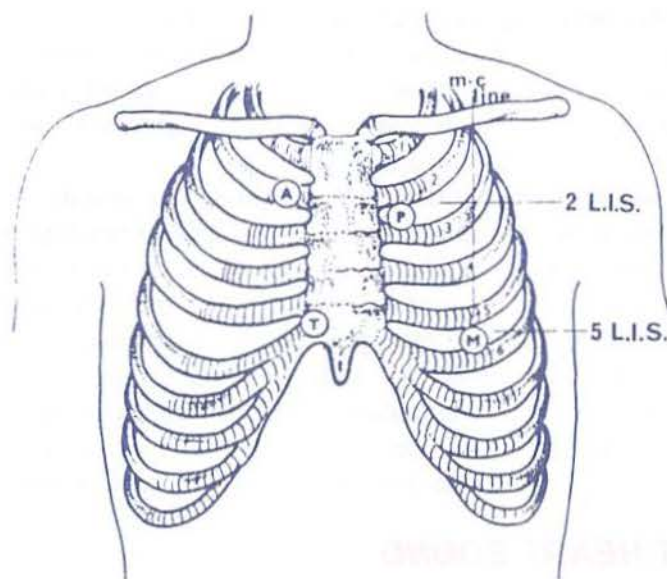


Figure 18 : Sites of hearing the heart sounds by the stethoscope.
 M, T, A and P = Mitral, Tricuspid, Aortic and Pulmonary areas. 2 and 5 L.I.S.= 2nd and 5th left intercostal spaces, m.c. line = midclavicular line.

THE SECOND HEART SOUND

Timing in the cardiac cycle : This sound coincides with the onset of ventricular diastole, so it falls during the *isometric relaxation phase* (figure 14).

Cause : Closure of the semilunar valves.

Mechanism : The sound is produced by the vibrations set up in the blood, ventricular walls and walls of the aorta and pulmonary artery after closure of the semilunar valves. It is *also not the result of snapping shut of the valves*

Characters : It is sharp and has a higher pitch than that of the first sound.

Duration : About 0.12 second.

Site of hearing : Closure of the aortic valve is heard over the second costal cartilage at the right sternal border, while closure of the pulmonary valve is heard at the second left intercostal space close to the sternum (figure 18).

Physiological splitting of the second heart sound

Normally, the **pulmonary valve closes after the aortic valve** (because the right ventricle is weaker than the left ventricle, so its systole is longer)

leading to splitting of the second sound. Such splitting is **more apparent during deep inspiration** because this increases the venous return which further delays closure of the pulmonary valve (= **physiological splitting**). In addition, splitting of the second sound is characterized by the following :

- (1) It is *easier to hear than splitting of the first sound* (because closure of the semilunar valves produces high pitched sounds).
- (2) It is heard almost *only at the pulmonary area* (because closure of the aortic valve is audible in all areas of the precordium while closure of the pulmonary valve is heard only close to the pulmonary area).
- (3) It is *more easily heard in children* and it may be inaudible in older individuals specially males (due to muscle noise and the thick chest wall).

Paradoxical splitting of the second heart sound

This is a condition in which the **pulmonary valve closes before the aortic valve**. It is characteristic of *left ventricular failure* (due to the slower ejection from the left ventricle than normal which delays closure of the aortic valve). In this case, *deep inspiration does not increase splitting of the second sound but rather decreases it* (= **paradoxical splitting**).

THE THIRD HEART SOUND

This is a soft low pitched sound that occurs during the **rapid filling phase of the cardiac cycle** (figure 14). It is produced as a result of oscillation of the rushing blood from the atria into the ventricles. Its duration is about **0.1 second** and is best heard during expiration at the apex of the heart.

THE FOURTH HEART SOUND

This is a faint very low pitched sound that occurs during **atrial systole** and its mechanism is similar to that producing the third sound. Its duration is 0.03 - 0.05 second and is **normally inaudible** (see above).

GALLOP RHYTHM

In some heart diseases (specially *left ventricular failure*) and certain other conditions (e.g. severe anemia and thyrotoxicosis), the 3rd or 4th heart sound is augmented and becomes audible. On auscultating the heart in these conditions, more than 2 sounds will be heard during each cardiac cycle, and these sounds follow each other in a rhythm similar to that produced by a **galloping horse** (so it is referred to as a **gallop rhythm**).

HEART MURMURS

A heart murmur is an abnormal sound i.e. a sound that is **not normally present** (*in contrast to gallop*). They are produced when the normal silent (= laminar) blood flow is replaced by a turbulent (noisy) blood flow, which occurs when the blood velocity exceeds a certain limit (page 95). The blood velocity increases after an area of partial obstruction in a blood vessel and also as it passes through **stenotic or insufficient heart valves**. A stenotic valve is a stiff *narrowed valve that does not open completely* while an insufficient (or incompetent) valve is a *valve that does not close completely*.

TYPES OF HEART MURMURS

(1) Systolic murmurs : These occur during the ventricular systolic period (i.e. between the first and second sounds). They may occur *without* heart disease (e.g. in anemia, fevers and exercise) or as a result of valvular disorders produced by diseases (specially rheumatic fever) or congenital abnormalities. The valvular disorders that produce systolic murmurs are either :

(a) **Stenosis of one of the semilunar valves**

(b) **Incompetence of one of the AV valves** : This may occur due to scarring of the valve cusps or a disorder in the papillary muscle-chordae tendinae system. In these *leaky valves*, blood regurgitation occurs toward the atria during ventricular systole resulting in the abnormal sound.

(c) **Ventricular Septal Defect (VSD)** (a congenital abnormality).

(2) Diastolic murmurs : These occur during the ventricular diastolic period (i.e. between the second sound and the next first sound) as a result of either of the following valvular disorders :

(a) **Stenosis of one of the AV valves** (e.g. due to rheumatic fever).

(b) **Incompetence of one of the semilunar valves** : In aortic incompetence (which is commonly due to *syphilis*), blood regurgitates from the aorta into the left ventricle during ventricular diastole resulting in a murmur as well as *reduction of the diastolic pressure*. The systolic pressure also increases (because the left ventricle will eject a larger volume of blood than normal) so the *pulse pressure also increases* (see below).

(3) Continuous murmurs (during systole & diastole) e.g. in patent ductus arteriosus (since the aortic B.P. is always higher than the pulm. arterial B.P.).

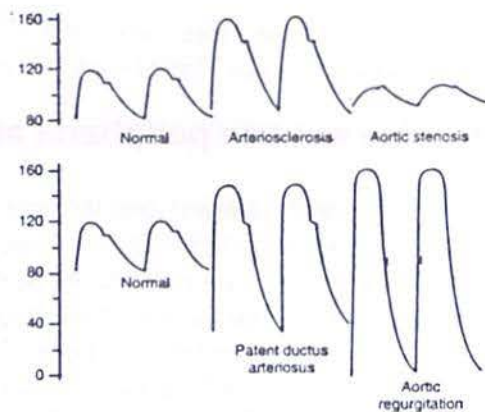


Figure 19 : The arterial pulse waves in various conditions.

THE ARTERIAL PULSE

This is the expansion of the arteries that occurs during left ventricular systole as a result of blood ejection. The ejected blood expands the proximal part of the aorta producing a **central pulse** which then sets up a **pressure wave** that travels along the arteries leading to their expansion which is called the **peripheral pulse**.

The rate of pulse wave transmission is *inversely proportional to the arterial wall compliance* (so it is about 4 meters / second in the aorta and 16 meters / second in the small arteries). It is also *much faster than the velocity of blood flow* (the velocity of the latter is only about 0.5 meter / second).

The arterial pulse wave

The normal arterial pulse wave (figure 19) is similar to the aortic pressure curve recorded during the cardiac cycle (figure 14), and it consists of :

(1) **An ascending limb (or anacrotic) limb** : This occurs during left ventricular systole as a result of rise of the arterial blood pressure produced by blood ejection into the aorta. The arterial blood pressure normally increases to a maximum of about 120 mmHg (= *systolic blood pressure*)

(2) **A descending (or catacrotic) limb** : This occurs during left ventricular diastole as a result of fall of the arterial blood pressure produced by escape of blood from the aorta to the peripheral arteries. The arterial blood pressure normally decreases to a minimum of about 80 mmHg (= *diastolic*)

blood pressure). As in the aortic pressure curve, the descending limb also contains a *dicrotic notch and a dicrotic wave* (+ several minor oscillations).

Changes in the pulse wave in peripheral arteries

The peripheral pulse is *normally delayed* than the central pulse by periods that vary according to the site of the artery (e.g. the pulse in the radial artery at the wrist is normally felt about 0.1 second after the peak of aortic pulse).

In addition, its shape is altered and its amplitude becomes progressively less as it travels into the peripheral vessels (*so capillary pulsations occur only if the aortic pulsations are extremely large or the arterioles are greatly dilated*). This is called **damping of the pressure pulses**, and is produced by the combined effect of the resistance to blood movement in the vessels as well as the compliance of the vessels.

****** In the femoral artery, the amplitude of the pulses rather increases probably by effect of *reflected waves from distal points in the arterial tree*. In addition, the incisura becomes less sharp but the *diastolic waves become more apparent particularly the dicrotic wave*.

The pulse pressure

This equals the difference between the systolic and diastolic pressures, so it is normally about **40 mmHg**. It *increases if the systolic pressure rises or the diastolic pressure falls (or both changes together) e.g. in cases of arteriosclerosis, patent ductus arteriosus and aortic regurgitation* (figure 19). Its magnitude is determined by 3 main factors which are the following:

- (1) The stroke volume.
- (2) The speed by which the stroke volume is ejected.
- (3) The compliance (distensibility) of the arteries.

The magnitude of the pulse pressure is directly proportional to the first 2 factors and inversely proportional to the third factor.

****** Absence of the pulse is *not always indicative of stoppage of blood flow* (if the mean arterial pressure is maintained normal at about 95 mm Hg, there will be an adequate blood flow although the pulse is not detected).

****** Examination of the arterial pulse gives information about the *heart rate and rhythm as well as the levels of the systolic and pulse pressures*.

Abnormal patterns of the arterial pulse

(1) **Pulsus alternans** (alternating large and small pulsations) : This is a sign of advanced left ventricular failure (specially if due to hypertension). It is

probably due to prolongation of the ARP in some myocardial fibres as a result of O₂ lack (page 14) which causes these fibres to respond only to every other impulse (so there will be alternating increase and decrease in the number of the contracting muscle fibres, which results in this type of pulse).

(2) **Pulse deficit** (the pulse rate is less than the heart rate) : This commonly occurs in cases of *extrasystoles* (page 15) and *atrial fibrillation* (page 61). In the latter condition, 2 heart beats frequently come so close to each other that the left ventricle will have too little time to fill between the beats. Accordingly, the 2nd beat pumps no (or very little) blood, which fails to produce an arterial pulse (although it produces heart sounds). Therefore, the pulse becomes irregular and its rate during a certain time will be less than the heart rate during the same time (normally both are equal).

(3) **Pulsus paradoxus** : Normally, the venous return increases during inspiration (due to the increased intrathoracic negativity) and this would increase the left ventricular stroke volume and the arterial pulse amplitude. However, this does not occur because the pulmonary vessels are also dilated due to the same cause, and will accommodate much of the right ventricular output, so the left ventricular stroke volume and the arterial pulse amplitude are normally kept constant or they may be slightly decreased.

Pulsus paradoxus means marked decrease of the arterial pulse amplitude during inspiration. It occurs in cardiac diseases that decrease the venous return e.g. *constrictive pericarditis* and *cardiac tamponade* (= cardiac compression) which is often due to a *massive pericardial effusion*.

(4) **Flat (plateau) pulse** : This is characteristic of *aortic stenosis* (figure 19). The pulse wave rises slowly to a lower amplitude than normal, and is also delayed than normal (so it is also called *pulsus tardus*).

(5) **Water hammer pulse (= Collapsing or Corrigan's pulse)** : This occurs in *all cases of increased pulse pressure* (page 40) specially aortic valve insufficiency (or incompetence). In the latter case, the pulse waves rise sharply to a high volume then rapidly collapse (i.e. fall abruptly) as a result of sudden drop from a high systolic pressure to a very low diastolic pressure (due to blood regurgitation into the left ventricle) and the dicrotic notch and dicrotic wave disappear (figure 19). The systolic ejection of blood may also be strong enough to cause head nodding with each heart beat.

(6) **Thready pulse** (i.e. very rapid - low amplitude pulse waves) : This specially occurs after a severe hemorrhage as well as in heart failure.

THE JUGULAR VENOUS PULSE (J.V.P.)

The J.V.P. is the pressure changes that occur in the jugular veins during the cardiac cycle. It can be seen by the naked eye and can also be recorded (the record is called the *phlebogram*). It consists of 3 positive waves (called

the **a, c and v waves**) and 2 depressions (called the **x and y descents**). Such changes are **transmitted from the right atrium** because there are no valves at the entry of the venae cavae into the right atrium, so they are similar to the atrial pressure changes (figure 14) but they are **slightly delayed** (figure 20).

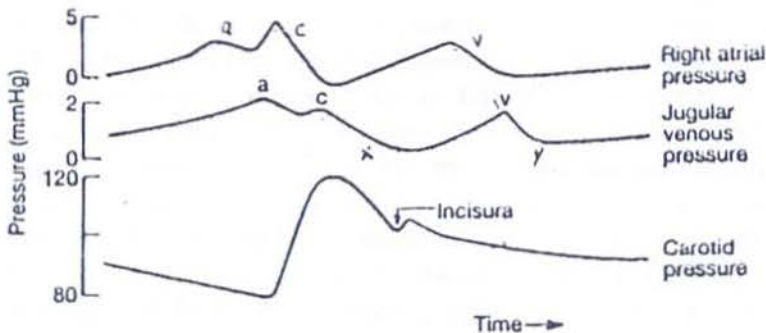


Figure 20 : Record of the J.V.P, carotid pressure and right atrial pressure

THE (a) WAVE

This wave occurs during **atrial systole**. Its ascending limb is due to (1) Increase of the right atrial pressure (which is transmitted to the jugular veins) (2) *Damming* (or accumulation) of blood in the jugular veins (due to constriction of the orifices of the venae cavae during atrial systole). On the other hand, its descending limb is due to decrease of the right atrial pressure as blood leaves the right atrium and enters the right ventricle.

THE (c) WAVE

The ascending limb of this wave occurs during **isovolumetric ventricular contraction** due to (1) Bulging of the tricuspid valve into the right atrium (which increases the right atrial pressure). (2) The **carotid artery pulsations** (which are transmitted to the jugular veins). On the other hand, its *descending limb and the x descent* occur during **early ejection** due to *increase in the right atrial capacity* (which decreases the right atrial pressure) as a result of (1) Atrial relaxation (diastole) (2) Pulling of the A-V ring downward during ventricular systole (3) Descent of the tricuspid valve to its normal position as blood is pumped out from the right ventricle..

THE (v) WAVE

The ascending limb of this wave occurs during **most of the ejection phases of the cardiac cycle as well as the isovolumetric relaxation phase** due to increase of the right atrial pressure as a result of accumulation of the venous blood returned to the right atrium while the tricuspid valve is closed. On the other hand, its *descending limb and the y descent* occur during the **rapid filling phase** due to drop of the right atrial pressure as a result of opening of the tricuspid valve and rush of blood into the right ventricle.

CLINICAL SIGNIFICANCE OF THE JVP

(A) The **a-c interval** (from the start of the "a" wave to the start of the "c" wave) is an *index of conductivity through the A-V node*. It corresponds to the *P-R interval of the ECG*, and its normal duration is **0.12 - 0.21 second**.

(B) The J.V.P. waves are altered in many cardiac diseases, so its recording is helpful in the diagnosis of these diseases. For example :

(1) Large "c" and "v" waves are recorded in cases of **tricuspid incompetence** due to blood regurgitation from the right ventricle into the right atrium during ventricular systole.

(2) The "a" wave amplitude is much increased in cases of **tricuspid stenosis, pulmonary stenosis and pulmonary hypertension**.

(3) Giant "a" waves called **cannon waves** are recorded if the right atrium and right ventricle contract *at the same time* (so the tricuspid valve is closed leading to much rise of the right atrial pressure). This occurs in cases of A-V dissociation (e.g. in *complete heart block and ventricular tachycardia*).

(4) The "a" waves **disappear in atrial fibrillation** due to inefficient atrial contraction. However, in this case the number of the "c" and "v" waves is greater than normal but are quite irregular (page 61).

(5) Inspection of the J.V.P. can differentiate **atrial from ventricular extrasystoles** (atrial extrasystoles produce a J.V.P. that contains the "a" waves while ventricular extrasystoles produce a J.V.P. that lacks the "a" waves).

CHAPTER 4

THE ELECTROCARDIOGRAM (ECG) AND THE ARRHYTHMIAS

The electrical currents generated as a result of myocardial electrical activity (depolarization and repolarization) are conducted through the body fluids to the body surface where they can be detected and recorded. The record is called the ECG, and it evaluates the cardiac electric events (which greatly helps in the diagnosis of many cardiac diseases). The apparatus used is called the *electrocardiograph*, and it consists basically of a *sensitive galvanometer and 2 electrodes* (which are applied to the skin).

RECORDING OF THE ECG (THE ECG LEADS)

The 2 electrodes that record the ECG can be applied at many areas of the skin, and any particular arrangement of these electrodes is called a **lead**. 12 of such leads (sometimes more) are usually used to record the electric cardiac events from different situations. These ECG leads are 2 main types :

(A) Bipolar limb leads (standard limb leads of Einthoven)

These leads record the differences between the potentials in 2 limbs. **3 of such leads are recorded** (figure 21). which include :

- (1) **Lead I** : This records the difference between the potential in the left arm (LA) and that in the right arm (RA) i.e. $LA - RA$ or $VL - VR$ ($V = \text{voltage}$).
- (2) **Lead II** : This records the difference between the potential in the left leg (LL) and that in the right arm (RA) i.e. $LL - RA$ or $VF - VR$ ($F = \text{foot}$).
- (3) **Lead III** : This records the difference between the potential in the left leg (LL) and that in the left arm (LA) i.e. $LL - LA$ or $VF - VL$.

Einthoven's triangle

This is an imaginary equilateral triangle, the sides of which represent the 3 bipolar limb leads (figures 21 and 30) and the heart lies at its centre.

Einthoven's law

This law states that the sum of voltages in leads I and III equals the voltage in lead II (figure 30 b), and it can be used to calculate the voltage of a certain lead if the voltages of the other 2 leads are known.

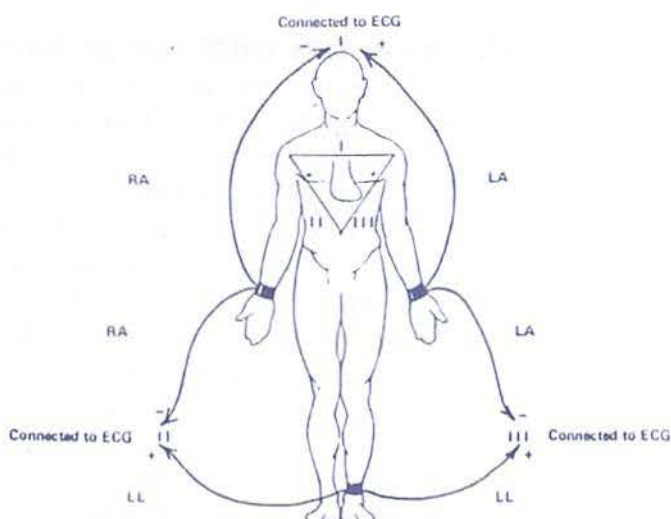


Figure 21 : The bipolar leads (standard limb leads).

(B) Unipolar leads

These measure the absolute (i.e. actual) potential at a certain point. This is carried out by applying one electrode from the electrocardiograph to the desired point (= +ve or *exploring electrode*) while the other electrode is made *indifferent* or -ve (i.e. at 0 potential). Therefore, a unipolar lead measures the difference between the potential recorded by the exploring electrode and zero potential.

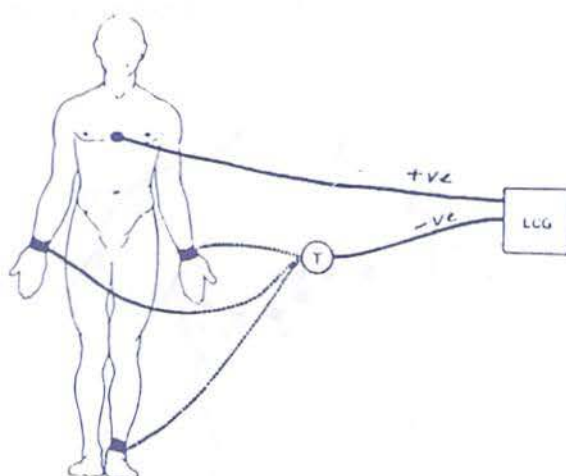


Figure 22 : Recording of the unipolar chest leads (T= central terminal)..

How can an ECG electrode be made indifferent (at 0 potential) ?

The potentials in a closed circuit neutralize each other, so their algebraic sum = zero. Electrodes from the 3 limbs that are connected to a common terminal constitute a closed circuit, so the potential at such common (or central) terminal will be zero. Therefore, when the central terminal is connected to the -ve pole of the electrocardiograph, it will constitute an indifferent electrode having zero potential (= Wilson's electrode), and in such case applying the exploring electrode (i.e. the electrode connected to the +ve pole of the electrocardiograph) at a certain point (whether at the limbs themselves or on the chest wall as shown in figure 22) will record the absolute potential at that point.

Types of unipolar leads

(1) **Unipolar limb leads** : These record the absolute potential at the right arm, left arm and left leg (by applying the +ve electrode at these limbs) and the potentials obtained are called **VR, VL and VF** respectively (figure 23).

(2) **Unipolar chest leads (Wilson's precordial or V leads)** : These record the absolute potential at 6 standard points on the anterior chest wall designated as **V₁ to V₆**, the locations of which are as follows (figure 23) :

V₁ : At the right margin of the sternum in the 4th right intercostal space.

V₂ : At the left margin of the sternum in the 4th left intercostal space.

V₃ : Midway between V₂ and V₄.

V₄ : At the left midclavicular line in the 5th intercostal space.

V₅ : At the left anterior axillary line and at the same level of V₄.

V₆ : At the left midaxillary line and at the same level of V₄ and V₅.

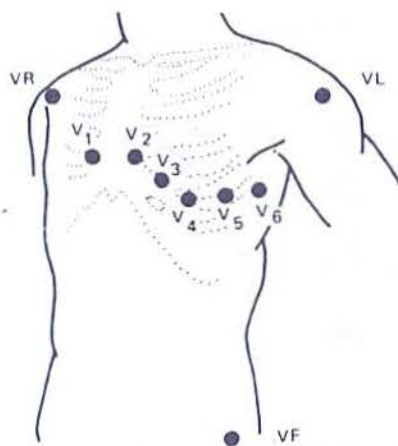


Figure 23 : Location of the exploring electrode in various unipolar leads.

The augmented unipolar limb leads (Goldberger's leads)

These are magnified unipolar limb leads (by 50 %) without change in configuration, so they are called **aVR**, **aVL** and **aVF** (a = augmented). They are easier to interpret and are routinely recorded by modern ECG machines. The augmentation of a unipolar limb lead is achieved by disconnecting its electrode from the central terminal. In this case, the augmented lead measures the difference between the potential in one limb and the sum of potentials in the other 2 limbs e.g. to record aVR, the electrode of the central terminal at the right arm is unattached (figure 24).

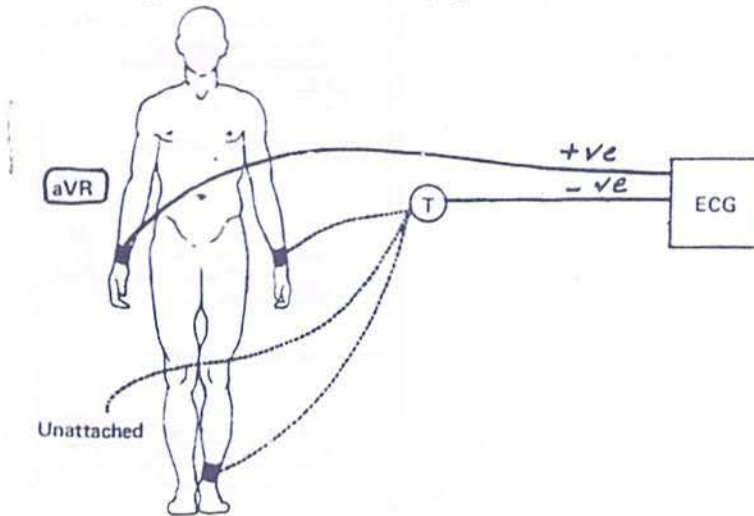


Figure 24 : Recording of augmented VR (aVR).

Calibration of the electrocardiograph

The electrocardiograph records *an upward (+ve) deflection when a depolarization wave moves toward the exploring electrode or a repolarization wave moves away from it, and vice versa* (figure 25). It is also arranged in a way that *a change of 1 mV produces a deflection of 10 mm amplitude*, so each mm in the vertical lines of the tracing paper (side of a small square) equals **0.1 mV**. On the other hand, the recording speed is usually **25 mm per second**, so the duration of each mm in the horizontal lines of the tracing paper (side of a small square) equals **0.04 second**, and the duration of each 5 mm (side of a big square) equals **0.2 second** (figure 27).

Calculation of the heart rate from the ECG

The duration of a single cardiac cycle is first determined (by multiplying the distance in mm between 2 successive R waves $\times 0.04$). The heart rate is then calculated by finding the number of cycles per minute (60 seconds) e.g. if the measured distance was 15 mm, the duration of a single cardiac cycle = $15 \times 0.04 = 0.6$ second and the heart rate = $60 / 0.6 = 100$ beats / minute.

****** The heart rate can also be determined by counting the number of small or big squares in the ECG paper as follows : When the recording speed is **25 mm per second**, one minute on the ECG paper will be represented by $25 \times 60 = 1500$ mm (i.e. 1500 small squares or 300 big squares). In this case, if the duration of one cardiac cycle was 15 mm (i.e. 15 small squares or 3 big squares), then the heart rate = $1500 / 15$ or $300 / 3 = 100$ beats / minute.

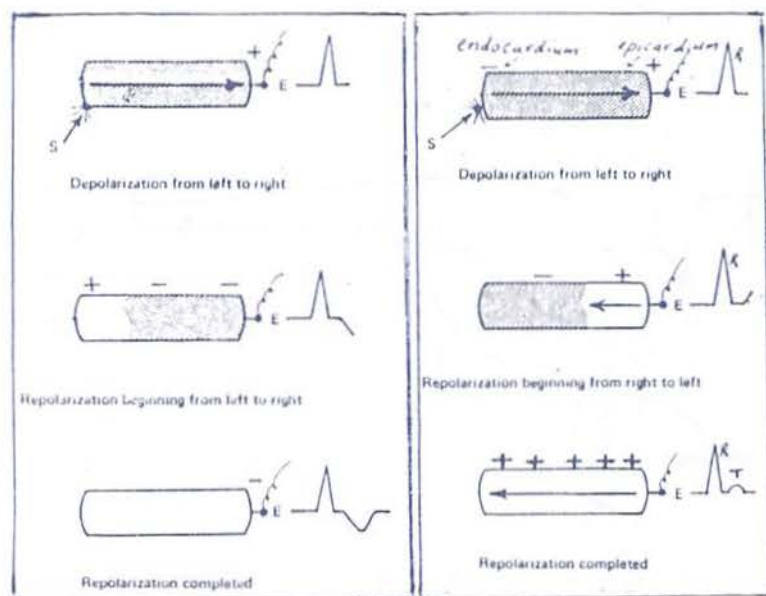


Figure 25 : Deflections produced by depolarization and repolarization in skeletal m (left) and cardiac m (right). E = exploring electrode. S = stimulus.

Spread of cardiac excitation

Depolarization initiated in the S-A node spreads through the atria from right to left, then in the interventricular septum from left to right (by a twig from the left bundle branch). In the ventricular wall, it spreads from the **endocardial to the epicardial surface**, and the last parts to be depolarized are the posterobasal portion of the left ventricle, the pulmonary conus and the uppermost part of the interventricular septum (figure 26).

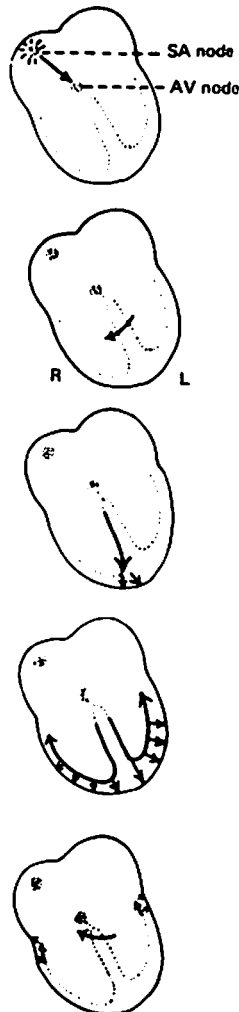


Figure 26 : Normal spread of electrical activity in the heart. The direction of the depolarization wave in each part is represented by an arrow (= vector).

THE NORMAL ELECTROCARDIOGRAM (ECG)

The ECG consists of 5 main waves called **P, Q, R, S and T waves**, and sometimes, there is an additional wave following the T wave called **U wave** (figure 27). Such waves are separated by segments, and each starts and ends at the isoelectric line. The Q, R & S waves form a complex called the **QRS complex**, and frequently the Q and S waves are normally not clear in some leads. The termination of the QRS complex at the isoelectric line is called the **J point**, and its determination is clinically important.

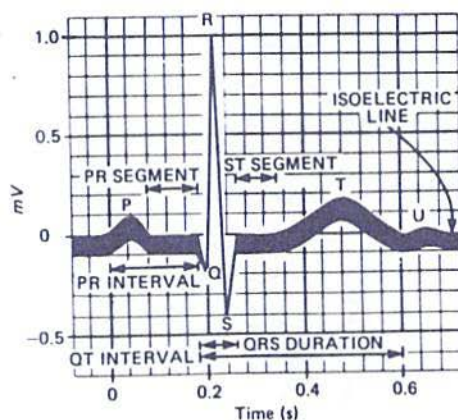


Figure 27 : A classic ECG tracing recorded from a left precordial lead (V_6).

P WAVE

This wave is produced as a result of *atrial depolarization*, and normally its amplitude is about 0.1 mV while its duration does not exceed 0.1 second. It is normally positive in all leads except aVR (page 53) *Its first part is due to right atrial activation while its terminal part is due to left atrial activation.*

Abnormalities of the P wave : In **left atrial hypertrophy** (e.g. due to mitral stenosis), the P waves enlarge and become notched (= **P mitrale**) and their duration increases because depolarization of the hypertrophied muscle takes more time than normal. In **right atrial hypertrophy** (e.g. due to tricuspid stenosis), the amplitude and duration of the right part of the P waves increase and overlap the left part, resulting in *tall peaked P waves* with almost normal duration (= **P pulmonale**). The P waves are also *inverted in AV nodal rhythm and disappear in atrial fibrillation* (page 61).

****** Normally, there is *no wave representing depolarization of the SA node* because excitation of this node does not generate sufficient electrical activity to reach the body surface. Also there is *no wave representing atrial repolarization* because it is normally small and is masked by the waves of ventricular depolarization (i.e. the QRS complex) which occur at the same time.

QRS COMPLEX

This wave is produced as a result of **ventricular depolarization** and its duration is **0.06-0.1 second**. *Depolarization of the interventricular septum produces the small Q wave, which is normally negative in the leads facing the left ventricle because the depolarization vector of the septum is directed from left to right (figure 26).*

The R wave is a large wave having an amplitude about 10 mm (1 mV) that is caused by *depolarization of the apex and ventricular wall*. It is +ve in the leads facing the left ventricle because ventricular depolarization proceeds from the endocardium towards the epicardium and the depolarization vector of the left ventricle predominates over that of the right ventricle (figure 26).

On the other hand, the S wave is due to *depolarization of the postero-basal part of the left ventricle and the pulmonary conus*, and it is normally negative in the leads facing the left ventricle because the depolarization vector of these areas is directed from left to right (figure 26).

****** The QRS amplitude is much larger than that of the P waves because the *ventricular muscle mass is greater* than that of the atria (so generating more electric activity). However, the duration of the QRS complex is almost equal or even shorter than that of the P waves because the *Purkinje system rapidly propagates excitation in the ventricles*.

Abnormalities of the QRS complex occur in cases of ventricular hypertrophy, infarction and extrasystoles, as well as in bundle branch block and most cases of electrolyte disturbance (see below).

T wave

This wave is produced as a result of **ventricular repolarization**. Its amplitude is **0.2 - 0.4 mV**, while its duration is **0.2 - 0.25 second** (longer than the QRS complex because *repolarization is slower than depolarization*).

Why the T wave is positive ? As a repolarization wave, the T wave should be negative (opposite to the depolarization wave, QRS complex). However it is **normally +ve** (figure 27) because the last part of the ventricular muscle to depolarize is the first part to repolarize, and thus *ventricular repolarization proceeds from the myocardial epicardial surface towards the endocardial surface, which results in an upright (+ve) deflection* (figure 25).

Repolarization fails to start at the myocardial endocardial surface probably as a result of **ischemia** (which may occur at this site due to the high ventricular pressure during ventricular systole that compresses the blood vessels).

Abnormalities of the T wave : The T wave becomes inverted (or isoelectric) in cases of myocardial ischemia, ventricular hypertrophy and extrasystoles, bundle branch block and digitalis overdosage. On the other hand, its amplitude increases in cases of sympathetic overactivity, muscular exercise and hyperkalemia (page 57).

U WAVE

This is a small positive wave that follows the T wave. It is probably produced by *slow repolarization of the Purkinje network*. However, it is not a constant finding and its physiological significance remains unsettled.

P- R INTERVAL

This is the interval from the start of the P wave to the start of the R wave (i.e. from the onset of atrial excitation to the onset of ventricular excitation). It normally ranges from **0.12 to 0.21 second**. This time involves conduction of the cardiac impulse through the AV nodal region, so it is an index for the duration of AV nodal delay. It is **prolonged** in (a) First degree heart block (b) Increased vagal tone, while it is **shortened** in (a) A-V nodal rhythm (b) Sympathetic overactivity (c) Wolff-Parkinson-White syndrome (page 65).

The P- R segment : This is a segment between the end of the P wave and start of ventricular depolarization. During this segment, depolarization occurs in the conducting system (*starting by the AV node at the top of the P wave*). However, it is silent (contains no waves) because the depolarized tissue is too small to generate electric changes great enough to reach the body surface.

Q-T INTERVAL

This is the interval from the onset of the Q wave to the end of the T wave. It is normally 0.3 - 0.4 second (varying inversely with the heart rate), and it provides an index of the duration of the ventricular action potential

S-T SEGMENT

This is the segment from the end of the S wave (J point) to the start of the T wave, and its duration normally averages 0.12 second. During this segment, *all ventricular fibres are depolarized*, so it is normally isoelectric and its deviation indicates myocardial injury or damage (page 56).

Time relation between the ECG and ventricular action potential

The QRS complex corresponds to the depolarization phase i.e. the upstroke of the action potential (phase 0), the S-T segment to the plateau phase (phase 2), the T wave to the repolarization phase (phase 3), and the T-P segment to phase 4 of the action potential. (figure 4 right).

Relation between ECG and the events of the cardiac cycle

The P wave precedes the atrial systole and the QRS complex precedes the isometric ventricular contraction (each by about 0.02 second). Also, *the first heart sound coincides with the summit of the R wave while the second heart sound coincides with the end of the T wave* (figure 14).

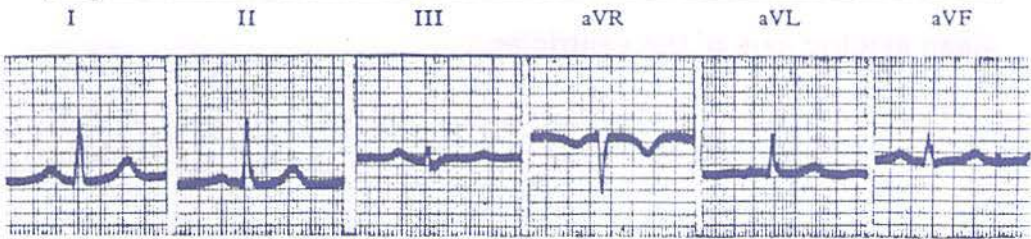


Figure 28 : An ECG of a normal adult man showing the records of the bipolar and unipolar limb leads (notice inversion of all waves in lead aVR).

Normal ECG variations in different leads

(1) Lead aVR : The P wave, QRS complex and T wave are all normally negative (inverted) deflections in lead aVR (figure 28) because the vectors of atrial and ventricular depolarization (figure 26) and that of ventricular repolarization move away from the exploring electrode at the right arm.

(2) The precordial leads : The electric forces of the heart act in the frontal, sagittal and horizontal directions, and the precordial leads look at the heart in a horizontal plane from the front and left sides. In the right precordial leads e.g. V₁ and V₂ (which look at the right ventricle), there are small R waves followed by deep S waves (figure 29), while in left precordial leads e.g. V₅ and V₆ (which look at the left ventricle), there are small Q waves followed by large R waves (figure 29). This is because :

(a) The excitation wave at the interventricular septum moves from left to right (figure 26), producing small +ve (R) waves in right precordial leads and small -ve (Q) waves in left precordial leads.

(b) Excitation then proceeds from the endocardial to the epicardial surface in both ventricles simultaneously (figure 26) As the left ventricular mass is greater than that of the right ventricle, the electrical changes occurring in the left ventricle predominate, so the ventricular depolarization vector is directed towards the left, producing large R waves in the left precordial leads and deep S waves in the right precordial leads.

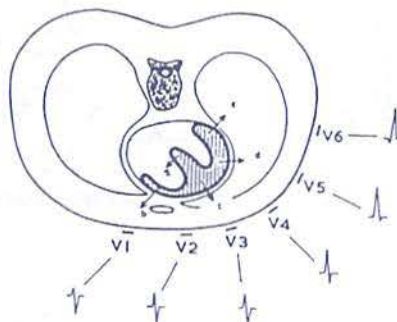


Figure 29 : Configuration of the QRS complex in the precordial leads (a, b, c, d & e show the order in which excitation spreads through the ventricles).

Mean electric axis of the ventricles

The depolarization wave in each cardiac muscle fibre is represented by an arrow pointing to the +ve direction (figure 25) called a **vector**, the magnitude and direction of which vary in different fibres. The vectors of all ventricular muscle fibres are represented by a single vector that can be determined from Einthoven's triangle (figure 30 a) and is called the **mean electric axis of the ventricles**. It represents an electromotive force that is normally directed downwards and to the left between -30° and $+110^\circ$ (figure 30 c) at an average of $+60^\circ$.

The projection of the electric axis is toward the +ve pole in the 3 bipolar limb leads, so +ve deflections are normally recorded in these leads. This is shown in figure 30 b (which also illustrates *Einthoven's law*, page 44).

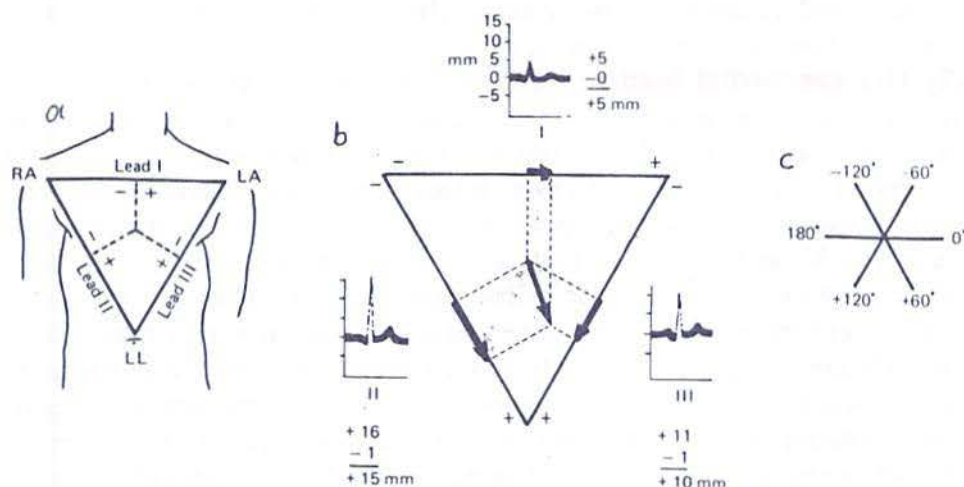


Figure 30 : The mean electric axis of the ventricles.

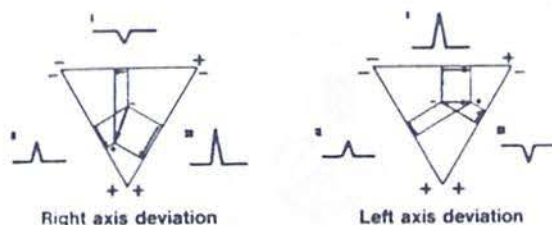


Figure 31 : Right and left axis deviation.

AXIS DEVIATION

The mean electric axis *may be shifted to the right or to the left*.

Right axis deviation normally occurs in vertical hearts (e.g. in tall subjects) but pathologically it occurs in many conditions particularly **right ventricular hypertrophy and right bundle branch block** (see below). In this case, the projection of the electric axis is toward the -ve pole in lead I and toward the +ve pole in lead III, so in ECG there are **deep S waves in lead I and high R waves in lead III** (figure 31).

Left axis deviation normally occurs in horizontal hearts (e.g. in short stout subjects and pregnant women) but pathologically it occurs in many conditions particularly **left ventricular hypertrophy and left bundle branch block** (see below). In this case, the projection of the electric axis is toward the +ve pole in lead I and toward the -ve pole in lead III, so in ECG there are **high R waves in lead I and deep S waves in lead III** (figure 31).

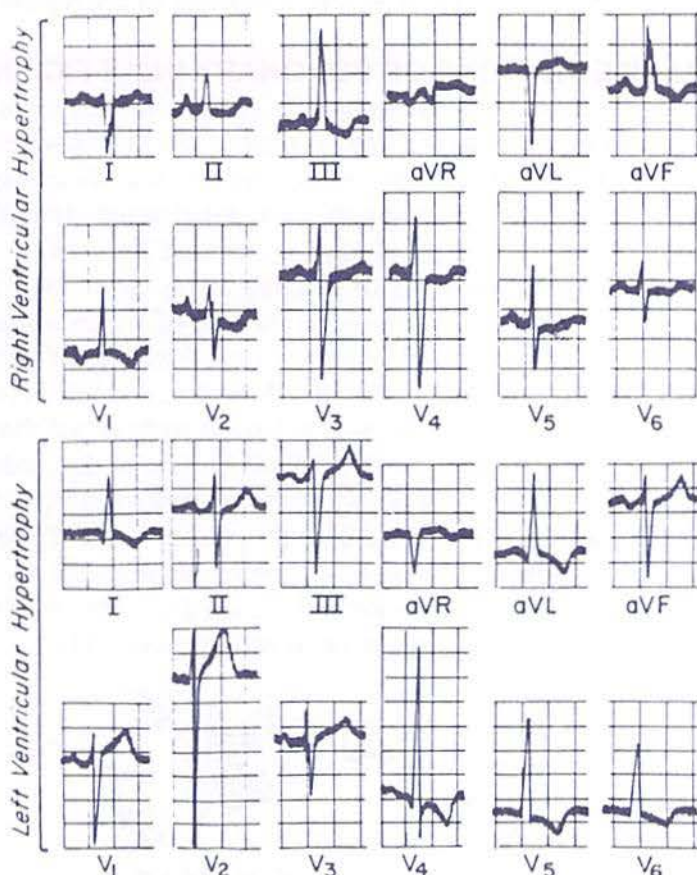


Figure 32 : ECG manifestations of right and left ventricular hypertrophy (the P waves may be normally inverted in lead V₁). Notice axis deviation.

ECG MANIFESTATIONS OF VENTRICULAR HYPERTROPHY

Left ventricular hypertrophy (figure 32) leads to (1) Appearance of high R waves in left precordial leads (V_5 and V_6) and deep S waves in right precordial leads (V_1 and V_2) (2) Inversion of T waves in the left precordial leads (due to relative ischemia of the increased muscle mass) (3) **Left axis deviation** *because the great muscle mass of the left ventricle allows (a) Generation of excess electrical currents in the left side of the heart (b) Complete depolarization of the right ventricle before the left ventricle, which creates a strong potential from the right side toward the left side of the heart.*

Right ventricular hypertrophy (figure 32) leads to (1) Appearance of high R waves in right precordial leads (V_1 and V_2) which exceed the depth of the S waves, together with deep S waves in left precordial leads (V_5 and V_6) (2) Inversion of T waves in the right precordial leads (due to relative ischemia of the increased muscle mass) (4) **Right axis deviation** (due to the same causes of left axis deviation in left ventricular hypertrophy).

ECG MANIFESTATIONS OF CORONARY INSUFFICIENCY

As a result of coronary insufficiency, the myocardium may suffer only ischemia but **injury or necrosis** (= death of muscle) occur in severe cases.

Manifestation of ischemia : The resulting hypoxia retards repolarization in the epicardial side of the affected part, so repolarization starts from the endocardium toward the epicardium producing *inverted T waves*.

Manifestation of injury (current of injury) : This causes *S-T segment shift* (elevation or depression depending on the site of the exploring electrode) as follows : *Injury of the cardiac muscle causes persistent depolarization in the affected part*, and this results in flow of a current between the pathologically depolarized and the normal polarized parts called the *current of injury*. This current leads to incomplete repolarization of the cardiac muscle, so the *T-P segment potential level becomes different from that of the S-T segment* (normally both are isoelectric) and this causes the *S-T segment to appear as if it was shifted*, although the shift was actually in the T-P segment. The latter is shifted downward in the leads facing the injury, so the ECG finding in these leads is *S-T segment elevation* (figure 34).

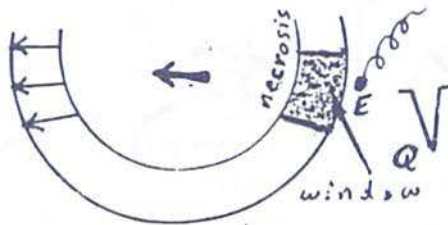


Figure 33 : Production of pathological Q wave due to myocardial infarction.

Manifestation of necrosis (= infarction) : This occurs almost always in the *left ventricular wall or interventricular septum or both* (right ventricular infarction is rare). The necrosed myocardium becomes electrically-inert and cannot be depolarized. If the whole free thickness of the left ventricular wall is necrosed, it creates *a hole or a window* through which an exploring electrode reflects the electrical activity of the distant healthy muscle in the interventricular septum and right ventricle. This results in recording of a **deep (= pathological) Q wave** (more than 0.2 mV) because the electric activity is directed away from the recording electrode (figure 33). If the necrosis was partial (e.g. subendocardial only), R waves will be recorded, the amplitude of which varies inversely with the extent of necrosis (figure 34).

An infarcted area due to *coronary heart disease* (= occlusion of the coronary arteries commonly as a result of thrombosis) consists of dead tissue (necrosis) surrounded by a zone of tissue injury, around which there is a zone of ischemic tissue (figure 34), so an electrode facing this area will record the ECG changes produced by these effects. In the acute stage, the first sign to appear (within a few minutes) is **S-T segment elevation** (injury). This is followed a few hours later by appearance of deep Q waves (necrosis) then by T wave inversion. After 1-2 weeks, the S-T segments become isoelectric again, and after a few months the T waves become upright. However, the **deep (pathological) Q waves persist and become permanent for life** (indicating presence of an old myocardial infarction).

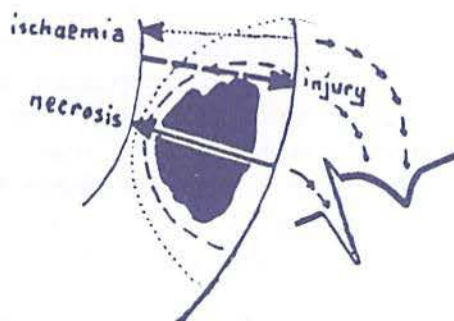


Figure 34 : ECG manifestations of coronary artery occlusion.

EFFECTS OF CHANGES IN SERUM Na^+ and K^+ LEVELS ON ECG

(1) Na^+ : Hyponatremia causes low-voltage QRS complexes while hypernatremia causes almost no effects.

(2) K^+ : The first ECG sign in hyperkalemia is appearance of **tall-peaked T waves** (disturbed repolarization). This is followed by absence of P waves (atrial arrest), S-T segment depression, prolongation of the QRS complexes and A-V block then by ventricular arrhythmia ending by its standstill. Hypokalemia is a less serious condition and is associated with prolongation of the P-R and Q-T intervals, prominent U waves and inversion of the T waves.

THE ARRHYTHMIAS (or DYSRHYTHMIAS)

These are abnormalities in the **number or regularity of heart beating**. Depending on the cause, cardiac arrhythmias can be classified into 2 types :

(1) Arrhythmias due to disturbances in impulse formation

These are produced as a result of either :

(a) **Alteration of S-A node rhythmicity** : These lead to the various **sinus rhythms** (which include *sinus tachycardia*, *sinus bradycardia*, *respiratory sinus arrhythmia* and *A-V nodal rhythm*)

(b) **Presence of ectopic foci** : In this case, impulses originate outside the S-A node and lead to the various **ectopic rhythms** (which include *extra-systoles*, *paroxysmal tachycardia*, *atrial and ventricular fibrillation*, as well as *atrial flutter*).

(2) Arrhythmias due to disturbances in impulse conduction

These are produced as a result of either *S-A block*, *A-V block* or the *Wolff-Parkinson-White syndrome* (see below).

Sinus tachycardia and sinus bradycardia

In sinus tachycardia, the pacemaker (S-A node) rhythmicity is stimulated e.g. in *muscular exercise* (due to increased sympathetic activity), and the heart rate increases to **100-120 / minute**. On the other hand, in sinus bradycardia, the S-A node rhythmicity is inhibited e.g. in *athletes* (due to increased vagal tone) and the heart rate is decreased **below 60 / minute**. In both conditions the ECG shows normal complexes but their rate is faster or slower than normal depending on the condition (figure 35)..



Figure 35 : (a) Sinus bradycardia (heart rate 50 /minute) and (b) Sinus tachycardia (heart rate 120 /minute).

Respiratory sinus arrhythmia

The heart rate is increased during inspiration and decreased during expiration. *The ECG shows normal complexes but their rate is faster or slower than normal depending on the respiratory phase.* It is a normal finding that commonly occurs in children and young adults, and it is due to *fluctuations in the strength of the vagal tone* that affects the the rate of S-A node rhythmicity (the causes of these fluctuations are discussed in detail on page 72).

A - V nodal rhythm

This condition occurs *when the A-V node becomes the pacemaker* following damage of the S-A node. The ECG shows (a) **Bradycardia** (because the A-V node rhythmicity is less than that of the S-A node) (b) **Short P-R intervals** (because the impulses reach the ventricles more rapidly than normal) (c) **Inverted P waves** (because the direction of atrial depolarization waves is reversed). The P waves are *frequently buried in the QRS complexes or they may follow the QRS complexes* (producing **negative P-R intervals**) *if the ventricles are excited before the atria* (figure 36).



Figure 36 : A-V nodal rhythm. Notice bradycardia (heart rate about 60/min) and inverted P waves following the QRS complexes (-ve P-R intervals).

Extrasystoles (or premature beats)

These are produced by impulses discharged *during normal SA rhythm* from ectopic foci that act as *pacemakers for only one beat*. In the ECG, they produce complexes *early in the T-P interval* (when the heart is totally repolarized). There are **2 main types of premature beats :**

(1) Supraventricular premature beats(figure 37a): These are produced by impulses discharged from ectopic foci in the *atria or A-V node*. The ECG shows (a) **Abnormal P wave** (commonly inverted) because the impulse spreads in the atria in an abnormal way (2) **Normal QRST waves** (the impulse spreads via the normal conducting system) (3) **Almost normal T-Q interval** because there is *no or short compensatory pause* (page 15). The P-R interval is shortened *if the ectopic focus was in or near to the A-V node*.

(2) **Ventricular premature beats** (figure 37 b) : These are produced by impulses discharged from ventricular ectopic foci. The ECG shows (a) Wide high abnormally-shaped QRS complex (= *bizarre QRS*) due to the relatively *slow conduction of the impulse through the ventricular muscle* (b) *No P wave* because the abnormal impulse is incapable of exciting the Purkinje-His system, so upward conduction to the atria does not occur (c) Prolongation of the following T-Q interval due to presence of *a complete compensatory pause* (d) *Inverted T wave* (e) *Axis deviation*.



Figure 37 : Supravent.(atrial) extrasystoles (a) and vent. extrasystoles (b).

Paroxysmal tachycardia

This is a pathological condition characterized by paroxysms (attacks) of tachycardia. It is due to activation of ectopic foci that discharge at a rate of **150-220 / minute** (average 200 / minute). Like extrasystoles, they may develop in the **atria, A-V node or the ventricles** (but unlike extrasystoles, they suppress the SA node during the attack and become the pacemaker instead) and accordingly, there are 2 main types of this arrhythmia :

(1) **Paroxysmal supraventricular tachycardia** : In ECG (figure 38 a), all complexes show *abnormal P waves* (like supraventricular extrasystoles). The atrial type may also occur in the *Wolff-Parkinson-White syndrome* (page 65) and is usually associated with some degree of A-V block (so the ventricular rate is only **170 -180 / minute** in most cases).

(2) **Paroxysmal ventricular tachycardia** : In ECG (figure 38 b), all complexes show *wide high bizarre-shaped QRS complexes and inverted T waves without preceding P waves* (like ventricular extrasystoles). The ventricular rate is **150-220 / minute** and this is more dangerous than the atrial type because (a) It leads to *marked reduction of the cardiac output* (b) It predisposes to *ventricular fibrillation*. Because the impulses cannot be conducted retrograde via the His-purkinje system, the atrial rhythm is normal i.e. it follows the S-A node rhythm (= **atrioventricular dissociation**).



Figure 38 : Paroxysmal atrial tachycardia (a) and vent. tachycardia (b).

Atrial flutter

This is a pathological condition in which the atria beat **regularly** at a rate of 250-350 / minute by impulses discharged from a hyperexcitable ectopic focus. As the A-V node cannot conduct more than 230 impulses / minute, **physiological incomplete heart block** develops, and the ventricles respond once for every 2 or 3 atrial beats. So in ECG, each 2 or 3 P waves are followed by one QRST, and the *P waves are abnormal* while the QRS and T waves are normal in shape and occur regularly but at a rapid rate (figure 39).

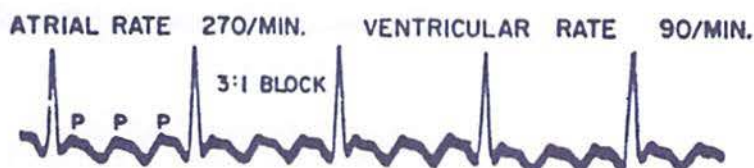


Figure 39 : An ECG showing atrial flutter (notice regular 3:1 A-V block).

Atrial fibrillation

This is a pathological condition in which the atria beat **irregularly** at a rate of 350-500/minute in response to impulses discharged from **multiple** ectopic foci or generated by **circus movement** (see below). Physiological heart block develops but **irregularly** (however, it is important since it **prevents development of ventricular fibrillation**). So the ventricles beat **irregularly** at a rate of 100-150 / minute and **pulse deficit** may occur (page 41). The atrial fibres contract **asynchronously**, so the atria appear as a **quivering bag of worms**. This leads to **inefficient atrial contraction** and blood stagnation in the atria which predisposes to **intra-atrial thrombosis** (this is dangerous because blood clots frequently detach and occlude important arteries). In ECG, there are no P waves (which are replaced by fine oscillations called **F waves**), and the QRS and T waves are normal in shape but irregular in rate (figure 40).



Figure 40 : An ECG showing atrial fibrillation (notice F waves and irregular QRS complexes).

Ventricular fibrillation

This occurs as a result of either **(1)** Impulses discharged from multiple ectopic foci (specially after an attack of paroxysmal ventricular tachycardia) **(2) Re-entry and circus movements of impulses** initiated by an electric shock or a premature impulse during the vulnerable period (see below) specially after myocardial infarction. It is **fatal** because it results in loss of the ventricular pumping power (which leads to stoppage of the circulation). In ECG, the QRS complexes are quite irregular in shape, rhythm and amplitude and all waves are not clear and cannot be identified (figure 41).

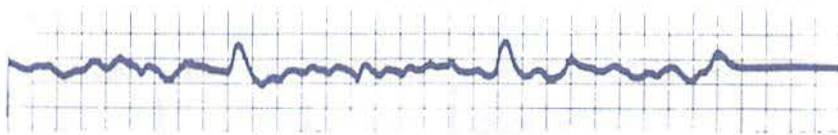


Figure 41 : An ECG showing vent. fibrillation ending by cardiac standstill.

The vulnerable period

This is a short period at the end of cardiac repolarization (during the early part of phase 4 of the action potential, page 13) that coincides with the **downslope of the T wave** (figure 4). It is a **dangerous period** because during it some fibres are completely repolarized and some are incompletely repolarized while few others are still depolarized, and this condition favours reentry and circus movements of impulses (see below) that may lead to ventricular fibrillation.

MECHANISMS THAT INITIATE ALTERATIONS IN CARDIAC RHYTHM

Alterations in the cardiac rhythm are produced by 2 main mechanisms : **(1)** Abnormal automaticity of the S-A node produced by changes in the slope of the prepotential (page 17) **(2)** The reentry phenomenon.

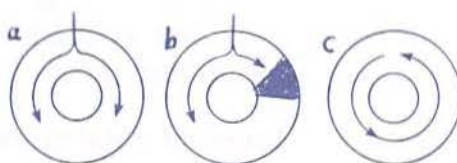


Figure 42 : Circus movement through a cardiac muscle strip. The shaded area in (b) is an area of block.

RE-ENTRY (CIRCUS MOVEMENT)

A circus movement develops when an impulse spreads in a circular pathway from a certain area of cardiac muscle then re-enters and re-excites the initial area, and this process is repeated resulting in continuous excitation. It is more liable to occur during the *vulnerable period* (see above) and by *application of a weak electric shock to the heart* (see below). The mechanisms of establishment of such circus movements are the following :

(1) In a circular cardiac muscle strip (figure 42), if there is a transient block at one side (e.g. due to ARP), an impulse will spread along the other side and on reaching the blocked area, the cause of block would have disappeared, so the impulse will re-enter the initial area and start a circus movement.

(2) In a circular cardiac muscle strip (figure 43), if the initially-stimulated area was recovered (i.e. becomes no longer in the ARP) on arrival of the impulse, the impulse will re-enter the initial area and start a circus movement. This is favoured when :

- (a) The length of the impulse pathway is prolonged (e.g. in dilated hearts).
- (b) The velocity of conduction of the impulse is decreased (e.g. in ischemia).
- (c) The ARP in the original area is shortened (e.g. by norepinephrine).

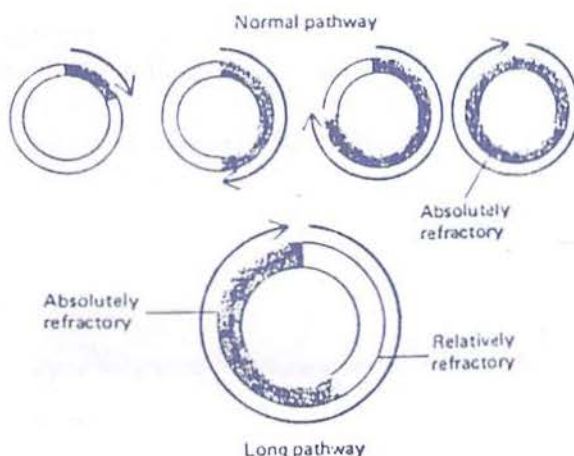


Figure 43 : Circus movement through a cardiac muscle strip.

****** The right atrial muscle that surrounds the openings of the 2 venae cavae is a common site for initiation of circus movements, and this may be responsible for production of atrial fibrillation and may also contribute in the production of atrial flutter and paroxysmal atrial tachycardia as well.

Physiologic basis of treatment of atrial flutter and fibrillation

- (1) **Quinidine** (prolongs the ARP, so it suppresses circus movements).
- (2) **B-receptor blockers** e.g. atenolol (decrease cardiac excitability).
- (3) **Digitalis** (decreases cardiac conductivity specially at the A-V node).
- (4) **Increasing the cardiac vagal discharge** e.g. by applying pressure on the eyeball (page 75) or massaging the carotid sinus (page 73).
- (5) **Cardiac defibrillation** (*applying strong electric currents to the heart*) : This maneuver can treat atrial flutter and fibrillation as well as ventricular tachycardia and fibrillation as follows : The strong current depolarizes all cardiac fibres simultaneously causing them to become refractory. As a result, all impulses from ectopic foci or initiated by reentry stop for a few seconds, after which the heart starts beating again by the S-A nodal rhythm.

****** While strong currents can treat ventricular fibrillation, **weak alternating currents may cause ventricular fibrillation**. This is because the depolarization wave produced by the current spreads in all directions leaving the muscle under the stimulating electrode in a refractory state. However, this muscle starts to recover after about 0.25 second, and some fibres recover earlier than others. This is an appropriate condition for *reentry and circus movements to develop* (see above) which lead to ventricular fibrillation.

ARRHYTHMIAS DUE TO CONDUCTIVITY DISTURBANCES

Sinoatrial block

This is often due to increased vagal tone. Some impulses *formed* in the S-A node *fail to be conducted to the atria*, resulting in **dropped beats** and absence of whole cycles (PQRST) in ECG (figure 44). Dropped beats are also encountered in cases of *sinoatrial arrest* (a disorder in the S-A node associated with failure of formation of impulses in the node while the ability of their conduction to the atria is normal)..



Figure 44 : ECG in case of sinoatrial block or arrest. Arrow = absent cycle.

****** Another disorder of the S-A node is the **sick sinus syndrome**, in which the node is affected by certain disease processes that lead to marked bradycardia. The main symptoms of this disorder are *dizziness and syncope (fainting)*, and it can be treated by implanting an *electronic pacemaker*.

Wolff-Parkinson-White syndrome (accelerated A-V conduction)

In the hearts of some individuals, there is a conducting muscular bundle between the atria and ventricles *in addition to the AV bundle*. This bundle is called the **bundle of Kent** and it conducts impulses *faster than the A-V bundle*. The cardiac impulses are conducted by **both bundles**, but since the bundle of Kent has a faster conductivity, one ventricle is excited earlier than the other, so the ECG shows wide slurred QRS complexes and short PR intervals with normal P waves (figure 45).



Figure 45 : An ECG in a case of Wolff-Parkinson-White syndrome.

This syndrome predisposes to paroxysmal atrial tachycardia *if an atrial premature beat occurs*. This is because the impulse that produces the atrial premature beat is conducted to the ventricles via the A-V node and when ventricular activation reaches the ventricular end of the bundle of Kent, this bundle will transmit the impulse retrograde to the atria and a circus movement will thus be established leading to atrial tachycardia. Less commonly, the premature beat is conducted to the ventricles via the bundle of Kent then transmitted retrograde to the atria via the AV node.

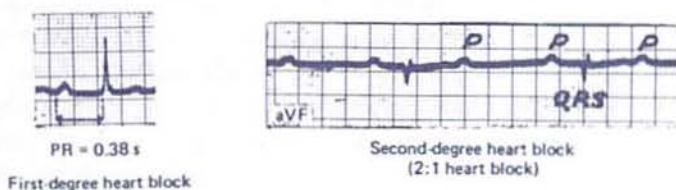


Figure 46 : First degree heart block(left) and 2nd degree heart block (right).

Atrioventricular (A-V or heart) block

This often results secondary to *ischemia of the A-V nodal or infranodal regions* and according to severity, there are 3 degrees :

(1) First degree heart block : This is the mildest degree. *All impulses are conducted to the ventricles, but much slower than normal.* It can be diagnosed *only from ECG*, in which it is indicated by prolongation of the P-R intervals more than 0.21 second (figure 46 left).

(2) Second degree heart block : In this type, the conduction through the A-V node fails intermittently, so in ECG some P waves are not followed by QRS complexes. This may occur irregularly leading to dropped ventricular contractions (*partial heart block*) or regularly (*incomplete heart block*). The latter may be 2:1 or 3:1 block i.e. a ventricular beat follows every second or third atrial beat, and in ECG there is one QRS complex for every 2 or 3 P waves (figure 46 right). However, in some cases, there is gradual prolongation of the P-R intervals in successive complexes till a P wave is not followed by a QRS complex and this process is repeated. Such case is known as **Wenckebach's phenomenon or block** (figure 47).

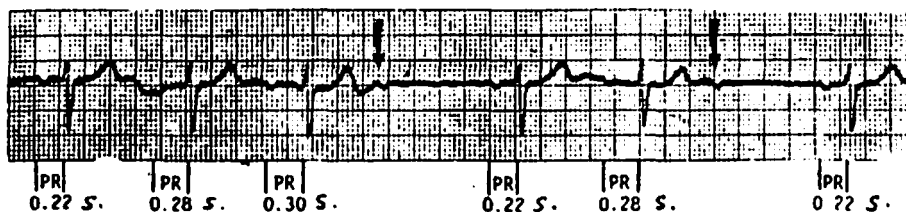


Figure 47 : Wenckebach's block. Arrows = P waves not followed by QRS.

(3) Third degree (or complete) heart block: This is the most severe degree in which impulse conduction through the A-V node is completely blocked. The atria beat regularly at a rate of about 70 / minute (the sinus rhythm) producing normal P waves in ECG. On the other hand, the ventricles also beat regularly but at a much slower rate (25-40 /minute) known as the **idioventricular rhythm** (which also often produces normal QRS complexes in ECG because it is initiated by impulses discharged from a latent pacemaker that develops in the bundle of His below the site of the lesion). However, the P waves and QRS complexes are *not related*, a condition called **A-V dissociation** (figure 48) as occurs in paroxysmal ventricular tachycardia (page 60). Complete heart block is often **incompatible with life**, and it can be treated by implanting an electric stimulator in the ventricles.

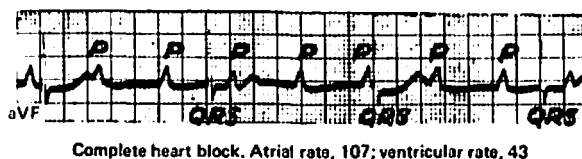


Figure 48 : An ECG showing 3rd degree heart block (note A-V dissociation).

Stokes - Adams syndrome

This is a condition in which there are periods of **ventricular asystole** that last a minute or more. It occurs in cases of prolonged S-A block as well as during transition from incomplete to complete heart block (due to delayed initiation of the idioventricular rhythm). It leads to marked decrease of the cardiac output, and the resulting *cerebral ischemia* causes dizziness then unconsciousness within 2 minutes, and death occurs if it lasts for a longer time.

Bundle branch block (BBB)

Injury of the right or left bundle branches is a serious condition that is commonly due to ischemia. It causes activation of one ventricle before the other because the depolarization wave reaches the affected side via the slowly-conducting ventricular muscle. It does not lead to arrhythmia but it can be **diagnosed from ECG**, in which the manifestations are due to the abnormal pathways of the depolarization and repolarization waves, and they include the following (figure 49) :

- (a) Prolonged slurred QRS complexes in various leads (more than 0.12 sec).
- (b) T wave inversion in the leads facing the affected side.
- (c) Right or left axis deviation (depending on the affected side).



Figure 49 : ECG manifestations in left BBB (note left axis deviation).

CHAPTER 5

THE HEART RATE

FUNCTIONS OF NERVES THAT SUPPLY THE HEART

(A) Functions of the cardiac sympathetic nerves

The sympathetic nerves supply all parts of the heart (atria, ventricles, conduction system and the coronary vessels). When activated, they lead to :

- (1) Increase of cardiac properties including (a) Rhythmicity i.e. the heart rate (+ *ve chronotropic effect*) (b) Contractility (+ *ve inotropic effect*) (c) Excitability (causing extrasystoles) (d) Conductivity (decreasing A-V nodal delay).
- (2) An increase of the cardiac output, heart work and O₂ consumption.
- (3) V.D. of the coronary vessels (*by the effect of metabolites*).

(B) Functions of the cardiac parasympathetic (vagal) nerves

These nerves supply the atria, the S-A and A-V nodes and the coronary vessels but **not the ventricles**. When activated, they lead to :

- (1) Depression of cardiac properties including (a) Rhythmicity i.e. the heart rate (-*ve chronotropic effect*) (b) Atrial contractility (c) Atrial excitability (so *it can stop atrial tachycardia and extrasystoles*) (d) Conductivity (it prolongs AV nodal delay and may produce heart block).
- (2) A decrease of the cardiac output, heart work and O₂ consumption.
- (3) V. D. of the coronary vessels.

****** The right sympathetic and vagus nerves influence the SA node while the left sympathetic and vagus nerves influence the AV node.

****** Both types of nerves also contain **afferent nerve fibres**. The sympathetic afferent fibres transmit pain signals from the heart while the vagal afferent fibres carry signals from atrial and ventricular receptors (see below).

THE CARDIOVASCULAR CENTRES

These are located in the reticular formation of the **medulla oblongata and lower part of the pons** and are also called the **vasomotor centre**. They regulate (control) both the *heart rate and contractility* as well as the *diameter of the arterioles and venules* through affecting the discharge in the *autonomic nerves that supply these structures*. They include a **sensory region** in the *nucleus of the tractus solitarius* (which receives the input signals to the centre) as well as the following centres (figure 50) :

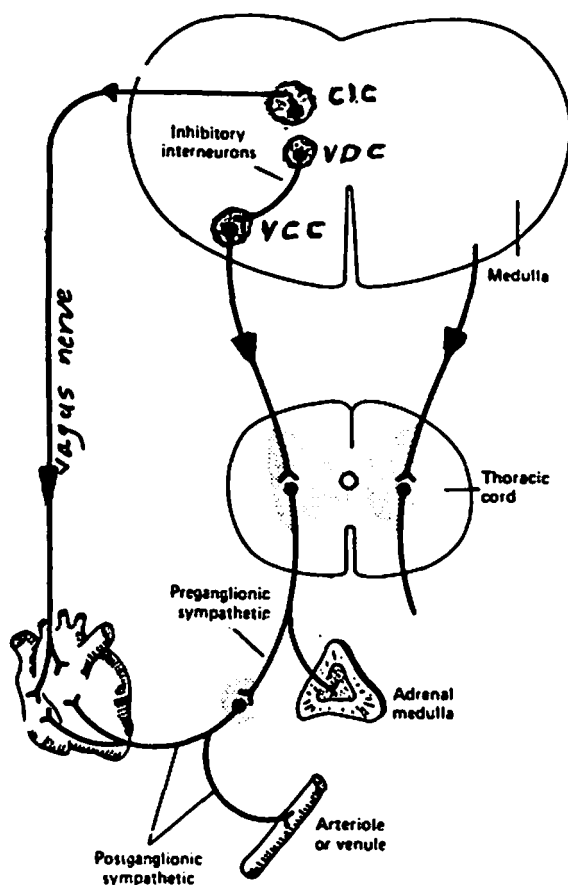


Figure 50 : Nerves that supply the heart and their central control.

(1) **Vasoconstrictor centre (VCC)** : Stimulation of this centre *increases the sympathetic discharge* to (a) All blood vessels (leading to generalized V.C.) (b) The adrenal medullae (leading to secretion of catecholamines) (c) The heart (leading to increase of the heart rate and cardiac contractility). The part of the VCC which produces these cardiac effects is sometimes called the **cardiac accelerator centre (CAC)**.

(2) **Vasodilator centre (VDC)** : Stimulation of this centre leads to generalized V.D. *through inhibiting the activity of the VCC*.

(3) **The cardiac centre** : This consists *mainly of a cardiac inhibitory centre (CIC)* which, when excited, *stimulates the adjacent nuclei of the vagi nerves*, and these in turn transmit signals that *decrease the heart rate and atrial contractility*. The CAC is related to the VCC as described above.

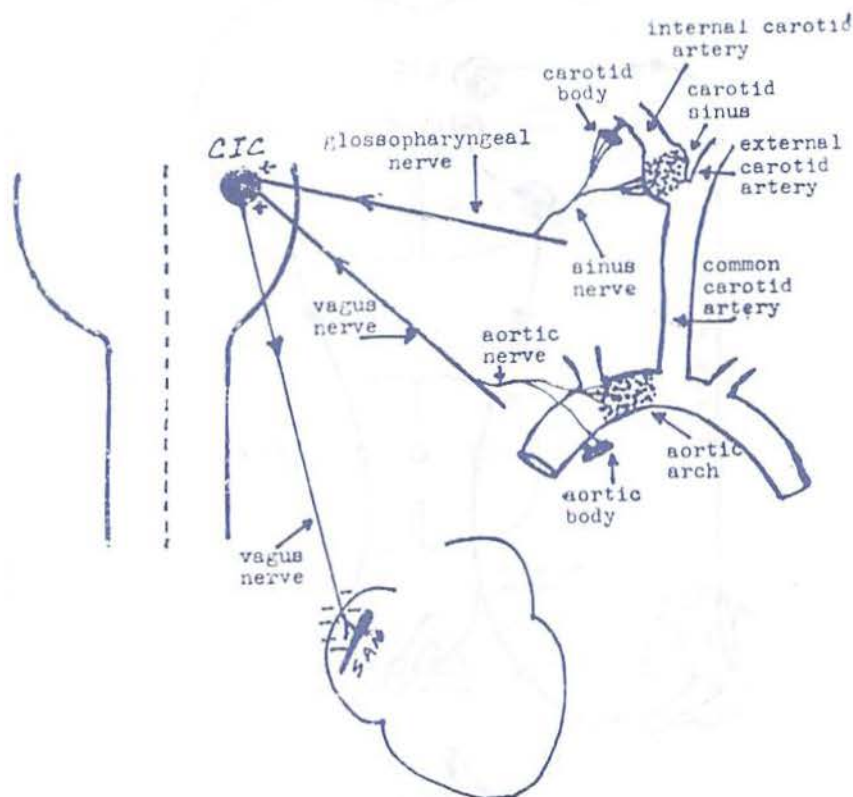


Figure 51 : The mechanism (pathway) of vagal tone on the heart.

THE SYMPATHETIC TONE ON THE HEART

This is *positively inotropic* (increasing the ventricular pumping power 20-25 %) and *positively chronotropic* (tending to increase the heart rate to about 150 / minute). However, the latter effect is antagonized by the more stronger vagal tone (see below). Thus, blocking the sympathetic activity decreases the ventricular pumping power 20-25 % but *has no effect on the heart rate*.

THE VAGAL TONE ON THE HEART

This is a continuous inhibitory effect exerted by the vagi nerves on the heart **during rest**. It dominates over the sympathetic tone at the S-A node, reducing its rhythmicity from about 100 to about 75 impulses / minute (but it *does not affect the ventricular pumping power* because the vagi do not supply the ventricles). Thus, *vagotomy leads to marked increase of the heart rate* (to about 150 beats / minute *by effect of the sympathetic tone*) as well as to a slight increase of the ventricular pumping power (*by effect of the increased heart rate*).

Mechanism (nervous pathway) of the vagal tone

The cardiac vagal tone is a **reflex** which occurs as follows (figure 51) : The *initiating stimulus* of the vagal tone on the heart is *the arterial blood pressure*. It stimulates certain stretch receptors located mainly in the walls of the *aortic arch and carotid sinus* called the **arterial baroreceptors or pressoreceptors** (page 102).

Impulses discharged from these receptors are conducted to the medulla oblongata via afferent nerve fibres in the *aortic and carotid sinus nerves* (which are branches of the *vagus and glossopharyngeal nerves* respectively). Such impulses *stimulate the CIC*, which in turn, discharges tonic impulses via efferent vagal nerve fibres that depress the inherent high autorhythmicity of the SA node (figure 51).

**** Complete denervation** of the heart increases the heart rate *only* to the inherent SAN autorhythmicity i.e. to about 100 beats / minute (and not to 150 beats / minute) due to loss of the sympathetic tone (which also decreases the ventricular pumping power by 20-25 %).

THE VAGAL ESCAPE

This refers to the *escape of the ventricles from the inhibitory effect of the vagi nerves*. Thus, after heart beating stops by a strong bilateral vagal stimulation, the ventricles start beating after a short time by their own **idioventricular rhythm** (25-40 / minute). This property is beneficial in cases of complete heart block in which the idioventricular rhythm cannot be decreased by vagal stimulation (but it can be increased by sympathetic stimulation because the ventricles are innervated by sympathetic nerves).

**** The aortic and carotid sinus nerves** also transmit impulses from the *peripheral chemoreceptors in the aortic and carotid bodies* (figure 51).

REGULATION (CONTROL) OF THE HEART RATE

The heart rate can be determined by counting *the arterial pulse, the heart sounds (using the stethoscope) or the ECG waves* and it normally averages 75 beats / minute (range 60-90 / minute) in young adult males during rest. It is basically determined by the *strength of the vagal tone*, and is subjected to **many physiological variations** such as (1) It is about 120 / minute in newly born infants (due to absence of the vagal tone) (2) It is more in females than in males (due to less vagal tone in females) and is *slowest in athletes* (due to a stronger vagal tone than in sedentary persons) (3) It shows *diurnal variations* (being lowest in the early morning) (4) It increases on changing from the recumbent to the upright posture (page 103).

The frequency of discharge of the S-A node (which determines the heart rate) is affected (or regulated) **by nervous and chemical factors**, as well as by certain other factors that directly affect the S-A node activity.

NERVOUS REGULATION OF THE HEART RATE

The heart rate is nervously regulated through the *cardiovascular centres* (see above) which control the *sympathetic and parasympathetic discharge* to the heart. The activity of these centres is affected by **(A)** Impulses discharged from certain supraspinal centres **(B)** Many reflexes initiated from the CVS itself as well as from several extravascular structures (see next).

(A) SUPRASPINAL CENTRES THAT AFFECT THE HEART RATE

(1) The cerebral cortex

The cortical influence on the heart rate is evident by alteration of the heart rate as a response in many *conditioned reflexes*. Also, through such cortical influence, some individuals can voluntarily control their heart rates.

(2) The hypothalamus and limbic system

These structures are concerned with *emotional reactions*. Most emotions are associated with tachycardia (e.g. before starting a race). However, severe emotions are frequently associated with bradycardia

(3) The respiratory centre

Respiratory sinus arrhythmia

This term refers to the increase of the heart rate during inspiration and its decrease during expiration that commonly occurs normally in young individuals and children (page 59). This phenomenon is primarily due to **fluctuations in the strength of the vagal tone to the heart during the respiratory cycle** which occur as follows : During inspiration, impulses discharged from the **inspiratory centre** and also in afferent vagal nerve fibres from certain **stretch receptors in the lungs**, *inhibit the CIC* so the cardiac vagal tone is decreased resulting in heart acceleration. During expiration, these impulses are no longer discharged, resulting in decrease of the heart rate.

(B) REFLEXES INITIATED FROM THE CVS

(1) Marey's reflex (Marey's law)

"A rise of the arterial blood pressure (ABP) leads to a decrease of the heart rate and vice versa, provided other factors affecting the heart rate remain constant". *It is initiated by stimulation of the arterial baroreceptors and its pathway is the same pathway of the vagal tone (page 71).*

Effects of stimulation of the arterial baroreceptors

- (1) Stimulation of both the CIC (resulting in reflex bradycardia) as well as the VDC (resulting in generalized V.D. and hypotension).
- (2) Inhibition of the respiratory centre (resulting in temporary apnea).
- (3) Inhibition of secretion of the antidiuretic hormone (ADH).

The carotid sinus syndrome

In some individuals, *the carotid sinus is abnormally hypersensitive* so that mild pressure on the carotid sinus behind the angle of the mandible (e.g. *during shaving or by a tight collar*) leads to bradycardia and generalized V.D. that may be severe enough to decrease the cardiac output and ABP to the extent of producing *brain ischemia and syncope* (fainting).

****** On the same basis, an attack of paroxysmal atrial tachycardia can be terminated through *initiating a carotid sinus reflex* (by light massaging of the carotid sinus, page 64).

(2) Bainbridge reflex

" *An increase in the right atrial pressure leads to heart acceleration* ". Impulses are discharged from special *tachycardia-producing atrial receptors* (see below) via afferent vagal nerve fibres to the medulla where they stimulate the CAC leading to heart acceleration. However, such response is not constant and its physiological role is not settled, and some authors believe that the resulting increase in the heart rate is due to *direct stimulation of the S-A node as a result of stretch*, and such effect is sometimes called the "Bainbridge effect".

Effects of rise of the right atrial pressure

(1) Tachycardia (*Bainbridge reflex*) (2) Tachypnea i.e. acceleration of breathing (previously called *Harrison's reflex*) (3) Generalized V.D. and decrease of the arterial blood pressure (4) Coronary V.D. (previously called *Anrep's reflex*) (5) *Inhibition of secretion of the antidiuretic hormone* (6) *Stimulation of secretion of the atrial natriuretic peptide (ANP).*

The atrial stretch receptors (baroreceptors)

- (1) **Type A** : These are **baroreceptors** that are stimulated when the *atrial pressure increases*.
- (2) **Type B** : These are **volume receptors** that are stimulated as a result of *distention of the atrial walls*.

As in case of the arterial baroreceptors, stimulation of both types of receptors leads to generalized V.D. and hypotension but sometimes with *tachycardia* (Bainbridge reflex) and *tachypnea* (Harrison's reflex), and *type A atrial receptors are probably responsible for the latter effects*.

(3) Reflexes from the left ventricle

(A) Distention of the left ventricle leads to bradycardia, temporary apnea, V.D. and hypotension. Such response is initiated by stimulation of **baroreceptors in the ventricular wall** (page 101) and its significance is unknown (however, it may have a role in maintenance of the vagal tone).

(B) The Bezold- Jarisch reflex (coronary chemoreflex)

Injection of certain substances (e.g. serotonin, veratridine or capsaicin) into the coronary arteries that supply the left ventricle leads to bradycardia, V.D. and hypotension through stimulation of certain ventricular chemoreceptors. Its significance is unknown, but it may be the cause of the severe hypotension that frequently follows myocardial infarction (in which case it is probably initiated by certain substances released from the infarcted tissue).

****** The cardiovascular centres are also reflexly controlled by impulses discharged from the peripheral chemoreceptors located in the **aortic and carotid bodies** (figure 51). These receptors are sensitive to changes in the blood levels of CO_2 , O_2 and H^+ (particularly O_2 lack) and will be discussed in detail with chemical regulation of the heart rate (page 75).

(C) REFLEXES INITIATED FROM EXTRA-VASCULAR STRUCTURES

(1) FROM THE LUNGS

(A) Stimulation of the **baroreceptors in the pulmonary vessels** (page 101) leads to temporary apnea, bradycardia, V.D. and hypotension. On the other hand, *lung inflation leads to the same effects* but is associated with *tachycardia* which is produced as a result of stimulation of certain **stretch receptors in the lungs** (refer to *respiratory sinus arrhythmia*, page 72).

(B) The pulmonary chemoreflex

*Injection of certain substances (e.g. serotonin or capsaicin) into the pulmonary vessels leads to bradycardia, V.D. and hypotension through stimulation of certain pulmonary chemoreceptors. It is similar to the **coronary chemoreflex** (see above) and its significance is also unknown.*

(2) FROM SKELETAL MUSCLES (ALAM-SMIRK REFLEX)

" Voluntary contraction of skeletal muscles leads to an increase of the heart rate ". Impulses are generated from receptors in the muscles and joints during contraction and are transmitted to the medulla oblongata where they stimulate the VCC and inhibit the CIC , resulting in acceleration of the heart.

(3) FROM THE SKIN AND VISCERA

Exposure to cold and moderate painful stimuli from the skin or viscera usually result in reflex increase of the heart rate. However, severe pain (specially from the viscera) is commonly associated with bradycardia.

(4) FROM THE EYES (OCULO-CARDIAC REFLEX)

" Applying pressure to the eyeball results in reflex decrease of the heart rate ". Impulses from the eye are transmitted to the nervous system where they stimulate the CIC . Such response can be used to terminate an attack of paroxysmal atrial (but not ventricular) tachycardia (page 64)..

****** Signals from certain sensitive areas in the body known as the **trigger areas** (e.g. the larynx, testes and epigastric region) also result in cardiac slowing, and *heavy blows to these areas may lead to cardiac arrest.*

CHEMICAL REGULATION OF THE HEART RATE**(A) EFFECT OF CHANGES IN BLOOD GASES****(1) O₂ lack (hypoxia)**

A moderate O₂ lack increases the heart rate by **(a) A direct mechanism** (stimulation of the S-A node activity) **(b) A central mechanism** (inhibition of the CIC) **(c) A reflex mechanism** (stimulation of the VCC through exciting the **peripheral chemoreceptors in the carotid and aortic bodies**).

On the other hand, *severe hypoxia decreases the heart rate due to inhibition of both the VCC as well as the S-A node activity.*

(2) CO₂ excess (hypercapnia) and H⁺ increase

A moderate hypercapnia and H⁺ increase (acidosis) increase the heart rate by the following mechanisms **(a) Inhibition of the CIC** (after an initial short period of stimulation) **(b) Stimulation of the VCC** through exciting the peri-

pheral chemoreceptors (specially by H^+ increase) (c) Stimulation of the VCC through exciting the **central chemoreceptors** (only by CO_2 excess).

On the other hand, *severe hypercapnia or acidosis* decrease the heart rate due to inhibition of the S-A node activity and paralysis of the VCC.

Effects of asphyxia on the heart rate : Asphyxia is associated with both hypoxia and hypercapnia, and it affects the heart rate as follows :

- (1) **Initial slowing** : This is due to the initial stimulation of the CIC and inhibition of the S-A node that are produced by hypercapnia (see above).
- (2) **Acceleration** : This is produced by the effects of mild hypoxia and also as a result of inhibition of the CIC induced by hypercapnia (see above).
- (3) **Premortal slowing** : This is due to inhibition of the S-A node and paralysis of the VCC induced by persistent hypoxia and hypercapnia.

(B) EFFECTS OF HORMONES, DRUGS AND CHEMICALS

- (1) **ADRENALINE** : Small doses increase the heart rate while large doses elevate the ABP which decreases the heart rate through the Marey's reflex.
- (2) **NORADRENALINE** : This is a potent V.C. hormone that markedly elevates the ABP, which decreases the heart rate through the Marey's reflex.
- (3) **THYROXINE** : This increases the heart rate by stimulation of the S-A node and increasing the metabolic rate (the formed metabolites cause V.D. which increases the venous return, resulting in the Bainbridge reflex)
- (4) **ATROPINE** : This accelerates the heart by blocking parasymp. activity.
- (5) **HISTAMINE** : This is a potent V.D. substance which leads to marked drop of the ABP, resulting in heart acceleration through the Marey's reflex.
- (6) **BILE SALTS** : These inhibit the S-A node activity and stimulate the CIC leading to bradycardia (refer to digestion).
- (7) **AUTONOMIC DRUGS**: Sympathomimetic drugs cause tachycardia while parasympathomimetic drugs cause bradycardia (refer to autonomic N.S.).

FACTORS THAT DIRECTLY AFFECT THE S- A NODE ACTIVITY

- (1) **PHYSICAL FACTORS** : An increase of the body temperature by one $^{\circ}C$ increases the heart rate by 10-20 beats / minute and vice versa.
- (2) **MECHANICAL FACTORS** : Right atrial distention may directly excite the S-A node leading to tachycardia (= **Baihbridge effect**, page 73).
- (3) **CHEMICAL FACTORS** : The S-A node is directly excited by mild hypoxia, catecholamines, thyroxine, certain electrolytes & in alkalemia, while it is directly inhibited by severe hypoxia & hypercapnia, bile salts, certain electrolytes, cholinergic drugs & in acidemia (see rhythmicity, page 18).

CHAPTER 6

THE CARDIAC OUTPUT AND VENOUS RETURN

Definition : The cardiac output (CO) is the amount of blood pumped by each ventricle per minute (so it is also called the *cardiac minute volume*).

Normal values : The normal CO at rest is *5 - 5.5 litres per minute*, and it is equal for both ventricles (page 86). The CO per square meter of body surface area is called the cardiac index, and its normal value in adults is about *3.2 litres / square meter / minute*.

The CO equals the product of the heart rate x stroke volume. The *stroke volume (SV) is the volume of blood pumped by each ventricle / beat* and it equals the *difference between the ventricular end diastolic and end systolic volumes (EDV and ESV respectively)*. The **EDV is the amount of blood in the ventricles at the end of diastole** while the **ESV is the amount of blood in the ventricles at the end of systole** (i.e. the amount of blood that remains in the ventricle after ejection). The normal EDV and ESV during rest average **130 ml and 50 ml** respectively. Thus, the average resting $SV = EDV - ESV = 130 - 50 = \text{about } 80 \text{ ml}$.

The ejection fraction (EF) : This is the percentage of the end diastolic blood volume that is ejected per beat. It equals the $SV / EDV \times 100$ and normally at rest, it averages $80 / 130 \times 100 = 65 \%$ (range 60 – 75 %) i.e. *only about 2/3 of the EDV is normally ejected during each systole*.

FACTORS THAT AFFECT THE END SYSTOLIC VOLUME (ESV)

These are the same factors that affect myocardial contractility (page 21). However, +ve inotropic factors decrease the ESV, and vice versa.

DIASTOLIC (RELAXATION) PROPERTIES OF THE VENTRICLES

Ventricular relaxation is important for normal cardiac function (like ventricular contraction) since deficient relaxation also decreases the SV and CO (due to impairment of ventricular filling). The process of ventricular relaxation is determined by both active and passive properties :

(1) Active relaxation property of the ventricles : This refers to the relaxation that occurs as a result of Ca^{2+} reuptake by the sarcoplasmic reticulum and is known as **lusitropy**. It is responsible for most of ventricular filling during early diastole, so positive lusitropic factors (e.g. most positive inotropic factors) increase ventricular filling.

(2) **Passive relaxation property of the ventricles** : This refers to the various mechanical factors that passively affect ventricular relaxation. These factors *affect the extent of ventricular filling* and include specially **ventricular compliance (= distensibility) and stiffness**. *The extent of ventricular relaxation is decreased if the ventricular compliance is decreased e.g. as a result of cardiac tamponade (see below) or increased ventricular stiffness (as occurs in cases of infarction and hypertrophy).*

FACTORS THAT AFFECT THE END DIASTOLIC VOLUME (EDV)

(1) **Atrial pressure** : This is the *filling pressure of the ventricles*. Its increase (e.g. as a result of atrial systole) increases the EDV and vice versa.

(2) **Blood volume** : Hypovolemia decreases the mean circulatory pressure (MCP, see below) resulting in reduction of the venous return (VR), atrial pressure and EDV. Hypervolemia produces opposite effects.

(3) **Venous tone** : Venoconstriction (by sympathetic stimulation) increases the MCP resulting in increase of the VR, atrial pressure and EDV.

(4) **Intrapericardial pressure** : Its increase e.g. as a result of fluid or blood accumulation (= *cardiac tamponade*) decreases the EDV (see above).

(5) **Atrial fibrillation** : This weakens atrial contraction, thus the booster pump function of the atria and the EDV are decreased (see below).

(6) **Intrathoracic pressure** : An increase of its negativity (e.g. in deep inspiration) increases the VR and promotes ventricular relaxation, and both effects increase the EDV. Opposite effects occur if its negativity is lost or becomes positive (e.g. in case of pneumothorax).

(7) **Muscle contraction** : This increases the VR, atrial pressure and EDV.

(8) **Posture** : In the upright position, blood pools in the lower limbs by the *effect of gravity*, thus the VR, atrial pressure and EDV tend to decrease (however, this is normally prevented by certain mechanisms, page 83).

(9) **Ventricular compliance and stiffness** : The EDV is directly proportional to the former and inversely proportional to the latter.

The booster pump function of the atria

Atrial systole enhances (adds to) the pump function of the ventricles because it favours ventricular filling. This is called the *booster pump function of the atria* (boost = increase the value), and is normally insignificant since it contributes for only 20-30 % of ventricular filling. However, such atrial booster effect increases and becomes important in 2 conditions :

(1) *When the venous return increases* : In this case, stretching of the right atrium increases its pumping power according to Starling law, which increases ventricular filling and consequently the SV and CO. .

(2) *When the heart rate increases* : In this case, the SV would decrease because the diastolic periods (during which ventricular filling occurs) are shortened. However, the atrial contractions become stronger (= **atrial kicks**) probably due to the force-frequency relationship (page 24), which favours ventricular filling, so the SV and CO are not decreased and may increase.

Consequently, loss of effective atrial contraction (e.g. in atrial fibrillation) reduces the heart's ability to increase the CO during stresses associated with increased VR and heart rate (e.g. muscular exercise and emotions).

METHODS OF MEASUREMENT OF CARDIAC OUTPUT

(1) **ECHOCARDIOGRAPHY** : This method is **non-invasive** (i.e. it doesn't involve insertion of a cardiac catheter or injection of chemicals). It records both the EDV and ESV, so the SV can be calculated, and the CO can then be obtained by multiplying the SV x heart rate (see above).

(2) **APPLICATION OF FICK'S PRINCIPLE** : The Fick's principle states that "*the amount of a substance taken by an organ /minute = arterial level of this substance - its venous level x blood flow in that organ /minute*". This principle can be used to calculate the **CO of the right ventricle** (which normally equals the CO of the left ventricle) by determination of the following :

(a) The total O₂ consumption / minute (normally 250 ml /minute);

(b) O₂ content in venous blood (known by analysis of blood obtained from the pulmonary trunk by a *cardiac catheter* and is normally 140 ml / litre).

(c) O₂ content in arterial blood (known by analysis of blood obtained from an artery by *puncture under local anaesthesia* and is normally 190 ml / litre).

By applying the Fick's principle, the amount of O₂ taken by the lungs per minute = arterio-venous O₂ difference x blood flow in the lungs per minute (the CO of the right ventricle) i.e. $250 = 190 - 140 \times \text{right ventricular CO}$. So the **right ventricular CO** = $250 / 190 - 140 = 250 / 50 = 5 \text{ litres / minute}$

(3) **INDICATOR DILUTION METHOD** : A known amount of a dye (or a radioactive isotope) is injected into an arm vein (say 5 mg), and its concentration is determined every 2 seconds in serial samples of arterial blood and plotted against time (figure 52). The concentration of the dye increases gradually to a maximum after which it declines then rises again (indicating its recirculation). The time of a single circulation of the dye through the heart (the end of which is indicated by re-rise of its concentration in the arterial blood) is determined by extrapolation of the curve as shown in figure 52.

The *average* concentration of the dye in the arterial blood is determined. Suppose it was 1.6 mg per litre, and if the time of a single circulation of the dye through the heart was 39 seconds **during rest**, then the blood flow from the left ventricle (i.e. its output) in 39 seconds = $5 / 1.6 = 3.1$ litres, and its output per minute = $3.1 \times 60 / 39 = 4.7$ litres.

****** During exercise, the time of a single circulation of the dye through the heart is shorter (9 seconds). In this case, if the average concentration of the dye in the arterial blood was 1.51 mg /litre, then the left vent. output in 9 seconds = $5 / 1.51 = 3.3$ litres and its output / minute = $3.3 \times 60/9 = 22$ litres

****** Another method that depends on dilution is the **thermodilution method** which involves injection of cold saline into the right atrium and detection of the change in the temperature of the pulmonary arterial blood.

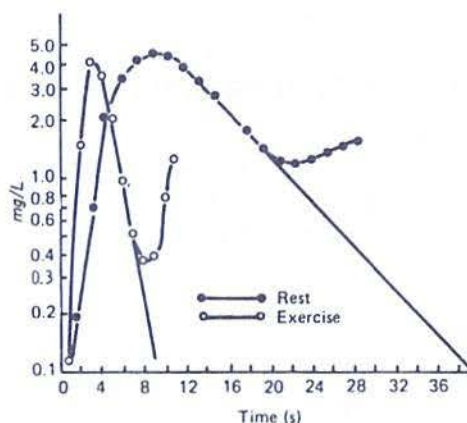


Figure 52 : Determination of the cardiac output by the dye dilution method.

FACTORS THAT AFFECT THE CARDIAC OUTPUT

The cardiac output (CO) is affected by changes in either the **heart rate (HR)** or the **stroke volume (SV)**, and such changes are regulated by both **extracardiac (extrinsic)** and **intracardiac (intrinsic) mechanisms** (page 84).

(A) EFFECTS OF CHANGES IN THE (HR) ON THE (CO)

(1) As the HR decreases below 70 beats / minute, the SV is increased (because the ventricles have enough time for maximum filling) and the CO remains almost constant.

(2) If the HR decreases below 50 beats / minute, the increase in the SV cannot compensate for the slowing of the heart, and the CO is decreased.

(3) As the HR increases from 70 to 180-200 beats / minute, the SV is decreased as a result of shortening of the diastolic periods (during which ventricular filling occurs). However, the CO remains constant or increases slightly due to heart acceleration.

(4) If the HR increases above 180-200 beats / minute, the diastolic periods become much shortened, so the SV is markedly decreased and the CO will also be decreased because the decrease in SV is not compensated by heart acceleration.

*** Therefore, both excessive acceleration and slowing of the heart are associated with decrease of the CO.*

(B) FACTORS THAT AFFECT THE STROKE VOLUME

(1) THE CARDIAC PUMPING POWER

This is affected by the cardiac inotropic state, preload and afterload and the myocardial blood supply as well as by other factors e.g. it increases in cases of sympathetic overactivity and ventricular hypertrophy, and decreases in cases of severe loss of the functioning myocardium (e.g. as a result of massive infarction).

(2) THE VENOUS RETURN (VR) (= CARDIAC INPUT)

The VR is a *basic determinant of the SV and CO*. It acts by affecting the EDV through the *Starling law*, and its volume is affected by the following factors :

(a) The *mean circulatory pressure* (MCP) or *mean systemic filling pressure* (MSFP) : This is the mean pressure in the systemic circulation. It *reflects the degree of filling of the circulation* and its magnitude is directly proportional to the blood volume and inversely proportional to the venous capacity. Normally, it is **7-10 mmHg** and the VR is directly proportional to it.

(b) The *right atrial pressure* (RAP) : This is normally about 2 mmHg during recumbency and 0 mmHg in the standing position, and the VR is inversely proportional to it.

(c) The *resistance to the VR* (R_V) : Normally, this is about 1.4 mmHg / litre of blood flow, and the VR is inversely proportional to it.

The relation between these factors is as follows :

$$VR = \frac{MCP - RAP}{R_V} \quad (\text{i.e. the VR is directly proportional to the difference between the MCP and RAP, and inversely proportional to the } R_V).$$

Permissive function of the heart

The term "permissive function" refers to the ability of the heart to act as a hydraulic pump that *permits pumping of variable amounts of VR*, and *under normal conditions, the CO is determined by the rate of VR and both are kept equal*.

During rest, the VR is 5- 5.5 litres / minute and an equal CO is ejected by the ventricles through their *intrinsic autoregulatory mechanisms* (page 85). These mechanisms aided by the sympathetic tone on the heart (page 70) can increase the CO up to 15-25 litres / minute e.g. during muscular exercise (= **cardiac permissive level**). Greater outputs more than the permissive level can still be ejected by (a) *Neuro-hormonal mechanisms* (increasing the sympathetic activity and secretion of catecholamines from the adrenal medulla) (b) *Cardiac hypertrophy* (which can increase the CO up to 35 litres / minute in well-trained athletes).

FACTORS THAT AFFECT THE VENOUS RETURN (VR)

(1) **Venous pressure gradient** : This is the *difference between the MCP and the right atrial pressure* and it is the *primary determinant of the VR (= cardiac input)*. *The greater this pressure gradient, the more becomes the VR, and vice versa.*

(2) **Skeletal muscle pump** : Skeletal muscle contraction compresses the veins inside them. This propels blood towards the heart, and retrograde flow (i.e. backflow of blood) is prevented by the *venous valves*. Such effect is also exerted, but to a little extent, by the *arterial pulsations*.

(3) **Respiratory pump** : During inspiration, the negativity of the intra-thoracic pressure increases, so the thoracic veins dilate and their resistance to blood flow is decreased. At the same time, the intra-abdominal pressure increases (due to descent of the diaphragm) which compresses and increases the pressure in the abdominal veins. The resulting increase in pressure gradient between the thoracic and abdominal veins helps VR towards the heart.

(4) **Venous (venomotor) tone** : This is a state of partial constriction of the venules during rest caused by continuous sympathetic discharge to these vessels. It creates an upstream pressure that maintains the VR against gravity.

(5) **Cardiac suction forces** : During ventricular systole, the downward movement of the A-V ring acts as a suction force that draws blood from the veins into the atria. Also during early ventricular diastole, the rapid ventricular expansion is associated with increased inflow from the filled atria, which decreases the atrial pressure resulting in suction of blood from the veins.

(6) **Blood volume** : A decrease of the blood volume (e.g. due to hemorrhage) decreases the MCP resulting in reduction of the VR, and vice versa.

(7) **Gravity** : This antagonizes the VR from the lower limbs. However, this effect is *normally antagonized by the thoracic and muscular pumps, the venomotor tone and the cardiac suction forces* (figure 53)..

(8) **Arteriolar and capillary diameters** : Arteriolar dilatation decreases the resistance to blood flow and increases the VR, and vice versa. On the other hand, severe capillary dilatation leads to pooling of blood in the capillaries, which decreases the MCP resulting in marked reduction of the VR.

(9) **Sympathetic stimulation** : This increases the VR by increasing the venous tone and the cardiac suction forces (see above) as well as by producing arteriolar V.D. in skeletal muscles.

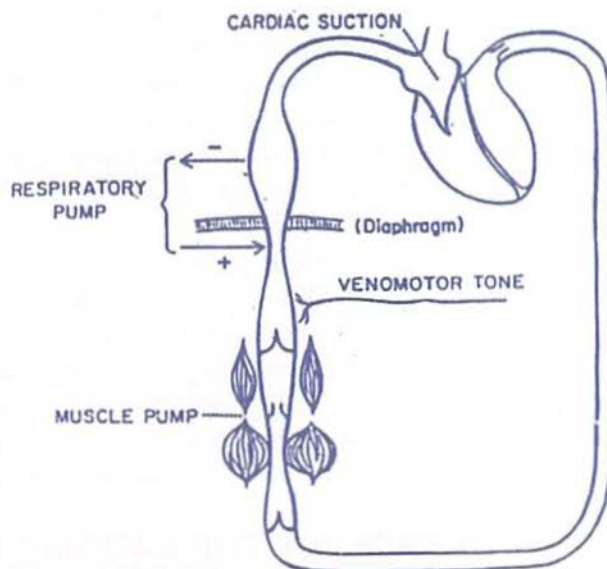


Figure 53 : Mechanisms that help the venous return from the lower limbs.

THE CENTRAL VENOUS PRESSURE (CVP)

This is the pressure in the *great thoracic veins at their entrance into the right atrium*. It is closely related to the right atrial pressure and both affect the CO directly and the VR inversely. It normally ranges from about 2 mmHg during standing to 4.6 mmHg in the recumbent position.

The cardiac-vascular coupling function of the CVP

The CVP acts as a **coupler** between the blood inflow from the vessels (VR) and the blood outflow from the heart (CO) which *allows intrinsic interaction between the cardiac and vascular functions*. Accordingly, its level is determined by the equilibrium between the VR and CO (e.g. it increases if the VR is increased with a constant or decreased CO, and decreases if the CO is increased with a constant or decreased VR), and at the same time, changes in the CVP causes alterations in the VR and CO.

DIFFERENCES BETWEEN the CVP and MCP

(1) The CVP is a *dynamic pressure* (recorded during the physiological state of the circulation), while the MCP is a *static pressure* (recorded only experimentally after stopping the cardiac input and output).

(2) The CVP *couple cardiac and vascular functions* while the MCP reflects the *degree of filling of the systemic circulation*.

(3) The CVP level is determined by the *ventricular pumping power, the VR and the blood volume*, while the MCP is determined by the *blood volume and venous capacity*.

(4) The CVP is **increased** in cases of *heart failure, increased intrathoracic or intrapericardial pressures, hypervolemia and if the VR increases* (e.g. by increased sympathetic activity), while the MCP is increased in cases of *hypervolemia and decreased venous capacity* (e.g. by sympathetic activity).

(5) The CVP is **decreased** in cases of *hypovolemia and venodilatation* as well as on standing (by the effect of gravity) and during deep inspiration while the MCP is decreased only in cases of *hypovolemia and venodilatation*.

REGULATION (CONTROL) OF THE CARDIAC OUTPUT

This occurs **through regulation of the stroke volume and heart rate**, and such regulation is produced by the following 2 mechanisms :

(1) EXTRINSIC REGULATION

This regulates *both the stroke volume and heart rate* by effect of :

(a) **The autonomic nerves** : Activation of the sympathetic system increases the CO as a result of increasing both the heart rate and SV, while parasympathetic activation decreases the CO by opposite effects.

(b) **Hormones** : Catecholamines and thyroxine increase the CO by exerting both + ve inotropic and + ve chronotropic effects (like sympathetic activity). Glucagon and insulin also exert a + ve inotropic effect (page 25).

(2) INTRINSIC REGULATION

This regulates the **stroke volume only**, and it includes **heterometric and homeometric regulation (or autoregulation)**.

(a) Heterometric autoregulation (Starling law)

This is regulation of the SV through changing the initial length of the muscle fibres. Filling of the ventricle leads to its expansion, thus the EDV and length of the muscle fibres increase, and according to Starling law, the force of contraction increases leading to an increase of the SV. This type of regulation occurs on increasing the **preload** and is **the first mechanism** for adjusting the CO according to changes in the venous return.

(b) Homeometric autoregulation

This is regulation of the SV **without a change in the length of muscle fibres**. A prolonged increase in EDV is followed by its decrease to its normal level while the ESV decreases less than its normal level by more forceful ventricular contraction, thus the SV remains elevated. This effect occurs on development of an **afterload** e.g. as a result of an increase in the aortic impedance secondary to rise of the arterial blood pressure. It may be due to either **(1) Increase of the coronary blood flow** as a result of the increased arterial blood pressure **(2) Laplace law** (which states that the ventricular wall tension is directly proportional to the intraventricular pressure).

The following table summarizes the main differences between heterometric and homeometric autoregulation of the cardiac output.

	Heterometric autoregulation	Homeometric autoregulation
Initiating stimulus	Increased EDV	Increased aortic impedance
Basis	Starling law	A change in cardiac inotropic state
Timing	Starts before homeometric autoregulation	Starts after heterometric autoregulation
Duration	Transient (short term)	Prolonged (long term).
Loading state	Preload phenomenon	Afterload phenomenon
Limit	The level of EDV	Available Ca^{+2} in the myocardium
Significance	Moment to moment adjustment of the VR and CO, and balance of the outputs of both ventricles.	Steady increase in the cardiac contractility with the increased aortic impedance

Physiological coordination of right and left ventricular pumps

Momentarily changes in the output of one ventricle are normally followed by similar changes in the output of the other so that *the blood flow rate in the systemic and pulmonary circulations is maintained equal*. This is carried out by cardiac and vascular mechanisms :

(1) Cardiac mechanism : This involves the *Frank-Starling mechanism*. Since the 2 ventricles are *connected in series*, a change in the ejected blood volume from the right ventricle leads to a corresponding change in the EDV of the left ventricle, resulting in a balanced outflow from the 2 ventricles.

(2) Vascular mechanisms : These include the following :

(a) The transmission of the right ventricular output via the pulmonary vessels to the left atrium is normally rapid enough to be synchronized with the left ventricular rapid filling phase (thus the EDV of the left ventricle is directly affected by the right ventricular outflow).

(b) The bronchial circulation (which is a part of the left ventricular output) serves to equalize the outputs of the 2 ventricles because it communicates with the pulmonary circulation via a physiologic shunt.

(c) The pulmonary circulation stores a variable amount of blood which can balance temporary differences in the outputs of the 2 ventricles after a few beats.

PHYSIOLOGICAL VARIATIONS OF THE CO

(1) Sleep : The CO remains *almost constant during calm sleep*.

(2) Posture : Changing from the recumbent to the upright posture tends to decrease the CO by about 30 % due to *decrease of the VR* as a result of pooling of blood in the lower limbs **by effect of gravity** . However, certain *compensatory mechanisms prevent the decrease of the VR* (page 83) and help maintenance of the CO and arterial blood pressure constant (page 126)..

(3) Meals : During the first few hours after meals, the CO is increased due to *increase of blood flow in the splanchnic circulation*.

(4) Temperature : At high environmental temp. (above 30 °C), the CO is increased due to increase of blood flow in the skin. It also increases at very low temp. due to *increase of the muscle tone & shivering* (see in metabolism)

(5) Pregnancy : The CO is markedly increased during pregnancy (specially in the later months) secondary to *the increased uterine blood flow*.

(6) Emotions : The CO increases up to 100 % in most emotions due to *stimulation of the sympathetic-adrenal system*.

(7) Muscular exercise : This produces the highest physiological increase in the CO. *It increases up to 7 folds or more in well-trained athletes*.

Relation between the right atrial pressure (RAP) and CO

The RAP is the filling pressure of the right ventricle. If the RAP increases, the right ventricular EDV, SV and CO will also increase, and this consequently leads to an increase of the left ventricular SV and CO. On the other hand, if the RAP is decreased, opposite effects occur. Such relation is shown in the **cardiac function (or cardiac output) curves** (figure 54).

The middle curve shows the cardiac function in the normal resting condition in the upright position (in which the RAP is about 0 mmHg and the CO about 5.5 litres / minute). The curve is **shifted upwards in hyper-effective hearts** (where at any given RAP, a greater CO is pumped) and **downwards in hypoeffective hearts** (where at any given RAP, a smaller CO is pumped). The main causes of hypereffective and hypoeffective hearts are shown in the following table :

HYPEREFFECTIVE HEART	HYPOEFFECTIVE HEART
Sympathetic stimulation	Parasympathetic stimulation or sympathetic denervation
Positive inotropic factors	Negative inotropic factors
Physiological cardiac hypertrophy (as occurs in well-trained athletes)	Heart weakening (e.g. due to ischemia, diphtheria toxin or myocarditis)
Decreased vascular resistance (e.g. due to a large arteriovenous fistula)	Increased vascular resistance (aortic impedance) e.g. due to hypertension
Increased heart rate	Heart block (and some arrhythmias)
Moderate change in blood temperature	Extreme change in blood temperature

Relation between the right atrial pressure (RAP) and VR

The volume of VR is directly proportional to the difference between the MCP and the RAP. Thus, a rise of the RAP is associated with a decrease of the VR and vice versa. Such relation is shown in the **venous return (or vascular function) curves** (figure 55a). The middle curve shows the normal resting conditions in the upright position, in which the MCP is 7 mmHg and the RAP 0 mmHg, and the VR about 5.5 litres /minute. It also shows that as the RAP increases, the VR is decreased till it stops when the RAP becomes 7 mmHg, at which the pressure gradient becomes zero. On the other hand, when the RAP decreases, the VR increases till it reaches a maximum then plateau at about -2 mmHg (because at such negative pressure, the intra-thoracic veins are collapsed, preventing further increase in the VR).

Effects of changes in the MCP : An increase of the MCP (e.g. by infusion of 2 litres of saline) shifts the curve upwards and to the right (upper curve in figure 55 a) indicating a greater VR than normal at any given RAP. On the other hand, a decrease of the MCP (e.g. after loss of 20 % of the blood volume) produces an opposite effect (lower curve in figure 55 a).

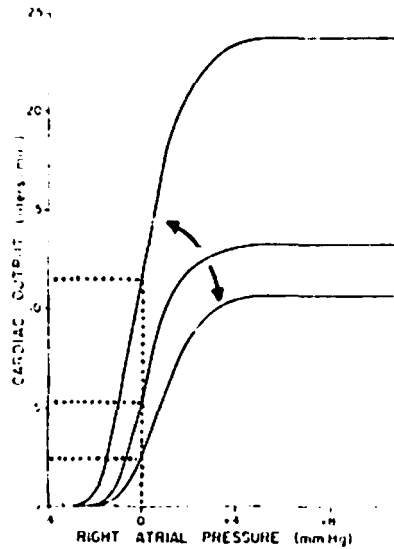


Figure 54 : The cardiac function (or cardiac output) curves.

Effects of changes in the resistance to venous return (R_V) : The VR varies inversely with the R_V (page 81). Thus a decrease of the R_V (e.g. due to presence of a large arteriovenous fistula) increases the slope of the venous return curve and rotates it upward and to the right (upper curve in figure 55 b), indicating a greater VR than normal at any given RAP without a change in the MCP. On the other hand, an increase of the R_V (e.g. due to compression of the inferior vena cava by a tumour) produces opposite effects (lower curve in figure 55 b).

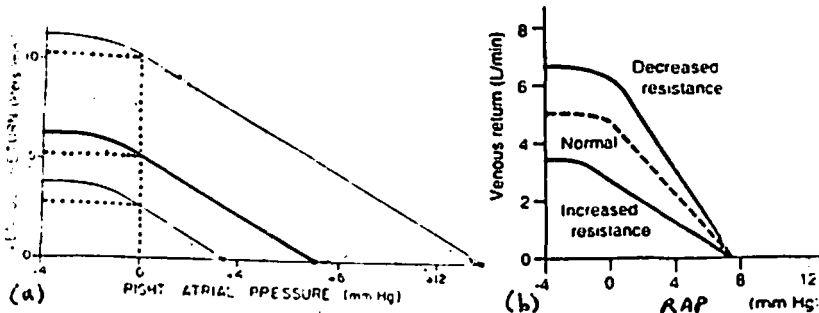


Figure 55 : The venous return (or vascular function) curves.

CHAPTER 7

THE CARDIAC ENERGETICS

CHARACTERISTICS OF CARDIAC MUSCLE METABOLISM

- (1) *A high rate of O_2 consumption* both at rest and during exercise.
- (2) *No O_2 debt* because energy production in the heart is almost completely dependent on aerobic (oxidative) metabolism.
- (3) *A high O_2 extraction ratio* (the cardiac muscle extracts 70-80 % of the arterial O_2 content at rest and greater amounts during exercise).
- (4) *A low venous O_2 reserve* (due to high O_2 extraction from arterial blood) *so extra O_2 can be supplied only by increasing the coronary blood flow.*
- (5) *Special metabolic substrates* : At rest, *fatty acids* are the main substances that supply energy. During exercise, *lactic acid and glucose* become also important energy producing substrates.

THE WORK OF THE HEART

The cardiac work is divided into 2 types :

(1) Internal work : This is the work done to generate tension in the ventricular walls. it is a *useless work* since it is not effective in blood movement.

(2) External work : This is used for ejection of a certain blood volume at a given pressure and with a certain velocity. It is the *effective (or useful) work* for the pump function of the heart, and is classified into 2 divisions :

(A) Pressure-volume work (= potential or pumping work) : This is the work done for ejection of the cardiac output against the arterial blood pressure. It constitutes 99 % of the external cardiac work and it consists of 2 parts

(a) Volume work i.e. the work used to eject the stroke volume

(b) Pressure work i.e. the work used to create pressure in the ejected blood volume. It is *much greater than the volume work*, thus a pressure overload (e.g. in aortic stenosis) is more exhaustive for ventricular function than a volume overload (e.g. in aortic regurgitation).

**** The stroke work (SW)** is the work done during a beat. It is calculated by multiplying the *SV x mean arterial blood pressure*, and is normally 0.93 and 0.14 Newton meter for the left and right ventricles respectively (the SW is lower in the right ventricle because the pulmonary arterial blood pressure is much lower than the systemic arterial blood pressure).

**** The minute work of a ventricle** (i.e. the work done per minute) = heart rate x (SW) of the ventricle = *cardiac output x mean blood pressure in the corresponding artery (aorta or pulmonary artery)*..

(B) Kinetic (acceleration) work : This is the work done to give velocity to the ejected blood in the vascular system. It constitutes *a minor fraction of the external cardiac work at rest* (only about 1 %) , and it is normally *equal in both ventricles* (about 0.009 Newton meter each). However, it is markedly increased during exercise.

****** The external cardiac work / beat during rest = $0.93 + 0.14 + (0.009 \times 2)$ = 1.088 Newton meter = 0.11 Kg.meter = about one joule.

THE CARDIAC RESERVE

DEFINITION : It is the ability of the heart to increase its work and output.

IMPORTANCE : The cardiac reserve is important for (1) Performance of severe muscular efforts (the cardiac output can be increased up to 35 litres in athletes) (2) Maintenance of efficient cardiac pumping in the early stages of some diseases e.g. hypertension, heart failure and most valvular diseases.

MECHANISMS OF THE CARDIAC RESERVE

(A) Heart rate (HR) reserve

Heart acceleration is the *first mechanism of the cardiac reserve*. The heart rate may increase during exercise to 180-220 beats /minute (by depression of the vagal tone and increasing sympathetic stimulation) with an increase of the CO about 3 times in untrained individuals and 5 times in athletes.

LIMITS : Tachycardia more than 220 beats / minute markedly shortens the diastolic periods, so ventricular filling, SV and CO will be decreased.

(B) Stroke volume (SV) reserve

The SV can be increased to 100 ml / beat or more, which results in increase of the ejection fraction and CO. This is achieved by **an increase of** (1) The **EDV** (in response to increase of the VR, which increases the SV through the Starling law) (2) **Power of ventricular contractility** (as a result of sympathetic stimulation).

LIMITS : Overstretch of the cardiac muscle fibres beyond an optimal length weakens myocardial contractility and decreases the SV (Starling law). The power of myocardial contractility is also *not unlimited*.

****** The SV can be doubled by simultaneous increase of the EDV (through Starling law) and decrease of the ESV (through increase of the power of myocardial contractility). During exercise, *the heart is insignificantly dilated* and its size actually decreases due to reduction of the ESV, indicating that the SV reserve is produced *mainly by increasing the power of contractility*.

(C) Cardiac hypertrophy

This results whenever the cardiac muscle fibres are exposed to **pressure or volume overloads** for long periods. In pathological states, it either increases the SV or keeps it constant. In case of pressure overloads (e.g. in hypertension and aortic stenosis), the left ventricular wall thickness increases while the EDV remains constant (= **concentric hypertrophy**). On the other hand, in case of volume overloads (e.g. in aortic regurgitation), the left ventricular wall thickness is not much increased while the EDV is markedly increased (= **eccentric hypertrophy**).

Cardiac hypertrophy also occurs normally with some ventricular dilatation in *highly-trained athletes* (producing what is called the *athlete's heart*). Such effect increases the power of cardiac contraction, the SV and the CO.

LIMITS : The cardiac hypertrophy reserve mechanism is limited by the available **myocardial blood supply**. *When the increased ventricular muscle mass exceeds a certain level, it will not be accompanied by a proportional increase in the myocardial blood flow, which decreases the cardiac performance and may lead to heart failure.*

(D) Other cardiac reserve mechanisms

These include mainly an increase of the coronary blood flow and the cardiac metabolic activity (page 131).

THE CARDIAC OXYGEN CONSUMPTION

During rest, a normal heart consumes about 29 ml O₂ / minute i.e. 11.6 % of the total O₂ consumption (250 ml/minute) although the heart constitutes about 0.05 % of the body weight (about 300 gm).

Determinants of the myocardial O₂ consumption

(1) **The heart rate :** The magnitude of myocardial O₂ consumption is directly proportionate to the heart rate.

(2) **Generated tension in the ventricular wall :** The magnitude of myocardial O₂ consumption is directly proportionate to the generated tension in the ventricular wall.

(3) **The stroke volume :** The ejection of the stroke volume requires much less O₂ than that required to develop tension in the ventricular wall (only about 15 % of the O₂ consumption).

(4) **The contractile (inotropic) state :** Enhanced myocardial contractility by + ve inotropic factors (e.g. sympathetic stimulation) is accompanied by an increase in O₂ consumption.

THE CARDIAC MECHANICAL EFFICIENCY (CME)

The CME is the % ratio of the useful (external) cardiac work to the total cardiac energy expenditure (or total O_2 consumption since the heart depends almost completely on O_2 for energy production). Normally, it is 15-25 % during rest, and it increases up to 40 % in muscular exercise.

FACTORS THAT AFFECT THE CME

(1) Type of contraction : During isometric contraction, the O_2 consumption increases to develop tension in the ventricular wall while no external work is done, so the CME is zero. On the other hand, during isotonic contraction (ejection phases), an external (useful) work is performed and the CME is increased.

(2) Type of work : The CME is higher when doing volume work (e.g. in case of muscular exercise and aortic regurgitation) than when doing pressure work (e.g. in hypertension and aortic stenosis) because the O_2 consumption is much smaller in case of volume work.

(3) The heart rate : The CME decreases in tachycardia because the myocardial O_2 consumption is markedly increased.

(4) Ventricular factors :

(a) Ventricular dilatation : This is a *disadvantage to ventricular function* because the ventricular radius is increased which according to the *law of Laplace* (page 93) *increases the tension required to produce a given intraventricular pressure*, so more internal work is done and the O_2 consumption is *markedly increased*, which tends to decrease the CME.

(b) Ventricular hypertrophy : This is an *advantage to ventricular function* because it increases the thickness of the ventricular wall, which according to the *law of Laplace* (page 93) *decreases the tension required to produce a given intraventricular pressure*, so less internal work is done and the O_2 consumption is *not much increased*, which tends to increase the CME.

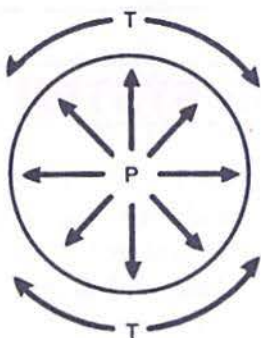


Figure 56 : The law of Laplace.

THE LAW OF LAPLACE

" The tension (T) developed in the wall of a hollow organ = Distending pressure (P) $\times$ radius of the organ (r) " i.e. $T = P \times r$ and $P = T/r$ (figure 56). It applies to several sites in the body e.g. *the urinary bladder, lung alveoli, stomach, blood vessels and heart*. In the heart, the element of *wall thickness* is also important, so the "**Laplace law of the heart**" states that *the tension (T) developed in the ventricular wall during ejection = intraventricular pressure (P) $\times$ ventricular radius (r) divided by the wall thickness (h)* i.e.

$$T = P \times r / h.$$

Application of Laplace law in increased ventricular afterload

The ventricular afterload is produced by (a) **Extracardiac factors**, mainly the *aortic impedance* (b) **Cardiac factors**, mainly the *ventricular diameter and the ventricular muscle mass* (i.e. the ventricular wall thickness). In these cases, Laplace law of the heart applies as follows :

(1) **Effect of aortic impedance** : Increased aortic impedance increases the intraventricular pressure (P) required to eject blood. This is a **disadvantage** because according to Laplace law, a greater tension (T) develops in the ventricular wall, so more energy (i.e. O_2) is consumed, resulting in reduction of the cardiac mechanical efficiency (page 92).

(2) **Effect of ventricular diameter** : Ventricular dilatation increases its radius (r) and decreases its thickness (h). This is a **disadvantage** because according to Laplace law, a greater tension (T) will be required to achieve a certain intraventricular pressure, so more internal work is done and the O_2 consumption is markedly increased, leading to reduction of the cardiac mechanical efficiency (page 92).

(3) **Effect of ventricular wall thickness** : Ventricular hypertrophy i.e. an increase in (h) is an **advantage** because according to Laplace law, a smaller tension (T) will be required to produce a certain intraventricular pressure, so less internal work is done and the O_2 consumption is not much increased, leading to elevation of the cardiac mechanical efficiency (page 92). However this occurs only if the blood supply is proportionately increased (page 91)

CHAPTER 8

THE VASCULAR SYSTEM BIOPHYSICS

The systemic circulation is made up of circuits of blood vessels that are *arranged in parallel* (figure 1), and each type of these vessels has a special characteristic and a peculiar function (page 3).

The blood flow rate (F) in blood vessels is directly proportionate to the pressure gradient (difference between the mean arterial blood pressure and the atrial pressure) and inversely proportionate to the peripheral resistance :

$$F = \frac{\text{pressure gradient}}{\text{peripheral resistance}}$$

In the systemic circulation, (F) = cardiac output (CO), and the pressure gradient = mean systemic arterial blood pressure (because the right atrial pressure is almost zero). Thus, $CO = \frac{\text{mean systemic arterial blood pressure}}{\text{peripheral resistance}}$

and mean systemic arterial blood pressure = CO x peripheral resistance

FACTORS THAT AFFECT THE PERIPHERAL RESISTANCE (R)

Most of the resistance to blood flow (R) occurs in the arterioles. From the *Poiseuille-Hagen formula*, $R = \frac{8 L n}{t r^4}$ where L = length of blood vessel,

n = blood viscosity, r = radius of blood vessel, and t = 3.14 (or 22 / 7).

Therefore, **the main factors that affect (R) include the following:**

- (1) The diameter (or radius) of the blood vessel.
- (2) The length of the blood vessel.
- (3) The blood viscosity.

The (R) is directly proportionate to the length of the vessel and the blood viscosity, and inversely proportionate to the 4th power of the radius of the vessel. Because the lengths of blood vessels are constant and the changes in viscosity are normally small, it follows that the *diameters of blood vessels constitute the main factor that regulates the peripheral resistance.*

****** Since the peripheral resistance (R) varies inversely with the 4th power of the radius (r) of the blood vessel, the (R) in vivo is markedly affected by small changes in the (r) e.g. if the (r) is doubled, the (R) is decreased to about 6 % of its previous value.

The unit of resistance (R unit) : This is the resistance that allows the flow of 1 ml blood /second at a pressure gradient of 1 mmHg. In the systemic circulation, the resistance is 1.1 R unit, while it is 0.14 R unit in the pulmonary circulation (i.e. about 1/7 that in the systemic circulation).

FACTORS THAT AFFECT THE BLOOD VISCOSITY

The blood has a viscosity about 3 - 4 times more than that of water, and is affected by the following factors :

(1) **The hematocrit (H)** : This is the main determinant of the blood viscosity. A high (H) increases the viscosity & peripheral resistance (e.g. in polycythemia and dehydration) while a low (H) decreases both (e.g. in anemia).

(2) **Composition of the plasma** : The plasma has a viscosity about 1.8 times more than that of water, which is primarily caused by fibrinogen and some globulins. Therefore, the blood viscosity is increased in cases of marked elevation of the plasma proteins (e.g. hyper-gammaglobulinemia).

(3) **Blood temperature** : Cooling increases the viscosity, and vice versa.

(4) **Diameter of the blood vessel** : The blood viscosity is low in the vessels having small diameters (due to a low (H) in these vessels).

(5) **Velocity of blood flow** : The viscosity increases at low velocity flow rates, and vice versa.

VELOCITY OF BLOOD FLOW

The blood velocity at any point in the circulatory system is **inversely proportionate to the total cross-sectional area** at that point, and is calculated by dividing the *blood flow rate / cross sectional area*.

In the aorta, the blood flow rate (= CO) is about 90 ml / second and its cross sectional area is about 4.5 cm^2 , thus the *blood velocity in the aorta is $90 / 4.5 = 20 \text{ cm / second}$* . In contrast, the total cross sectional area of the capillaries *if all are open* [which does not occur normally] is about 1000 times more than that of the aorta (4500 cm^2), thus the *blood velocity in the capillaries would be much slower ($90 / 4500 = 0.02 \text{ cm / second}$)*.

Estimation of the blood velocity

The blood velocity can be clinically estimated by measuring the circulation time between 2 points (i.e. the time taken by the blood to move from one point to the other) using certain substances, dyes or isotopes. For example ::

(1) **Arm to lung circulation time** : A few drops of ether are injected into an arm vein, and the time elapsing between the injection till smelling the odour of ether in the expired air is measured. Normally it is about **6 seconds**, and it indicates the pumping power of the right ventricle (so it is prolonged in right-sided heart failure).

(2) **Arm to tongue circulation time** : A bile salt preparation (decholin) is injected into an arm vein, and the time elapsing between the injection till the tasting its bitter taste is measured. Normally, it is about **15 seconds**, and it indicates the pumping power of *both ventricles* (so it is prolonged in both right and left sided heart failure, and if the arm to lung circulation time is normal, its prolongation indicates left sided heart failure).

****** The circulation times are also prolonged in cases of obstruction in the vascular system. On the other hand, they are shortened in cases of hyper-effective hearts (e.g. during exercise and in hyperthyroidism), and when the blood velocity is increased (e.g. in anemia).

TYPES OF BLOOD FLOW

(1) Laminar blood flow : This is the normal smooth (streamline) flow of blood in the blood vessels. It is silent (i.e. producing no sounds) and laminar i.e. the blood flows in several layers or laminae (figure 57 A). The outermost layer of blood in contact with the vessel wall is almost completely static (not moving) while the other layers move by velocities that increase gradually till becoming maximal in the central layer of the stream.

(2) Turbulent blood flow : This is disturbed blood flow in the form of eddies in various directions. It produces sounds (= *bruits or murmurs*) which can be heard by the stethoscope. It *specially occurs when a certain critical velocity of blood flow is exceeded*, in addition to other factors (see next).

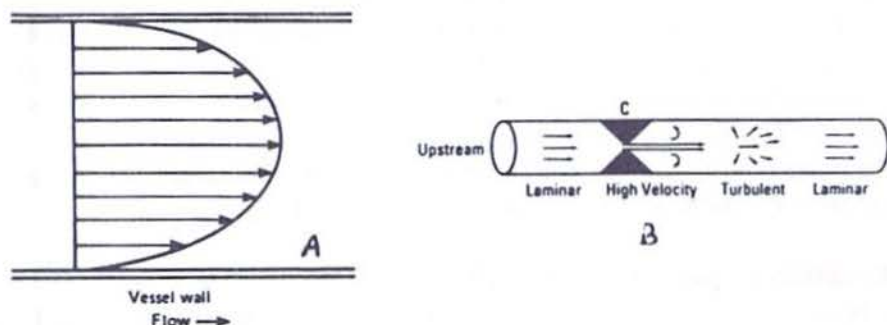


Figure 57 : Streamline (A) and turbulent (B) blood flow, c = constriction.

Probability of turbulence (The Reynold's number)

In addition to the blood velocity, its viscosity and density as well as the diameter of the vessel are also contributing factors in producing turbulence. The effects of these factors are expressed as the **Reynold's number (Re)**:

Re = pDV / n where p = blood density, D = diameter of the vessel, V = velocity of blood flow, and n = blood viscosity.

The higher the value of (Re), the greater the probability of turbulence.

In normal arteries, (Re) is 100 - 200, and turbulence starts if it exceeds 400. However, it is little as long as the (Re) is less than 2000 (but it becomes evident at higher values, specially if exceeding 3000).

Turbulence occurs **normally** at the branching of the vessels and at the roots of the aorta and pulmonary artery during the peak of systolic ejection (due to the increase in blood velocity). On the other hand, turbulence occurs **pathologically** due to increased blood velocity in the following conditions :

- (1) Beyond points of constriction in arteries (figure 57 B).
- (2) In severe anemia (in which the blood velocity increases due to reduction of its viscosity). In such cases, turbulence may produce *systolic murmurs*.
- (3) Stenotic and incompetent cardiac valves.

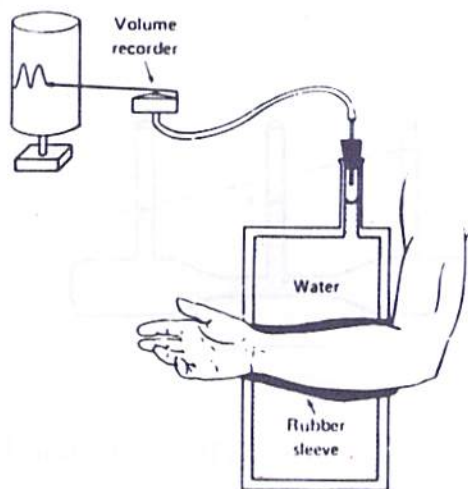


Figure 58 : Measurement of blood flow in the forearm by plethysmography

MEASUREMENT OF THE BLOOD FLOW RATE

This can be carried out by one of the following methods :

- (1) Using the electromagnetic or ultrasonic doppler flowmeter.
- (2) Applying the Fick's principle (page 79).
- (3) Determining the plasma clearance (for measuring the renal blood flow).
- (4) **Plethysmography** : The plethysmograph is a water-tight chamber by which the volume of an organ (e.g. the forearm) as well as its blood flow rate can be measured. The latter is carried out as follows : The forearm is placed in the chamber (figure 58) and its *venous drainage is occluded*. The increase in its volume / minute (which equals the amount of the displaced water) is measured, and is equivalent to the blood flow rate / minute.

The plethysmograph can also be used to (a) Demonstrate the phenomenon of *reactive hyperemia* (page 112) (b) Study the effects of various drugs on the arteriolar diameter (3) Detect the cause of an arterial occlusion (page 115).

The critical closing pressure

When the pressure inside a small blood vessel (= *intraluminal pressure*) is decreased, the blood flow is decreased proportionately till it stops completely *although the intraluminal pressure did not drop to zero*. The intraluminal pressure in this case is called the **critical closing pressure**, and the stoppage of blood flow is due to (a) The *extraluminal pressure* (= pressure exerted by the surrounding tissues) exceeds the intraluminal pressure resulting in collapse of the vessel (b) Drop of the intraluminal pressure below the pressure required to force the red blood cells through the narrow capillaries.

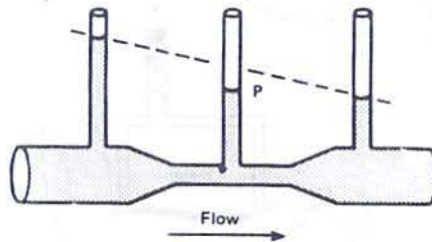


Figure 59 : Demonstration of Bernoulli's principle.

THE FLUID ENERGY and BERNOULLI'S PRINCIPLE

When fluid moves inside a tube, it acquires **2 types of energy** :

- (1) **Pressure energy (PE)** which causes lateral pressure on the tubular wall.
- (2) **Kinetic or flow energy (KE)** which moves the fluid along the tube.

The pressure gradually drops as the fluid moves along the tube (dashed line in figure 59) because of the energy lost in overcoming resistance (= frictional forces) and the energy that is converted into kinetic energy (since both types of energy are interchangeable). However, *the total energy at any portion of the tube (= sum of both types of energy) is constant, and this is called Bernoulli's principle*. According to this principle (a) If the kinetic energy (i.e. the velocity of flow) increases at a point (e.g. in a constricted part of the vessel), the pressure is further decreased (middle column in figure 59) (b) In a severely-dilated area of an artery (= *aneurysm*), the velocity is decreased while the pressure increases (so these areas are liable to rupture).

CHAPTER 9

THE ARTERIAL BLOOD PRESSURE

This is the force exerted by the blood on the arterial walls. It normally oscillates during the cardiac cycle between a maximum called the **systolic B.P.** (at the peak of the maximum ejection phase) and a minimum called the **diastolic B.P.** (just before opening of the aortic valve). The systemic systolic B.P. normally averages 120 mmHg in young adult males (range 100-140 mmHg), and is produced by *ejection of blood into the aorta during left ventricular systole*. On the other hand, the systemic diastolic B.P. normally averages 80 mmHg (range 60-90 mmHg), and is produced as a result of the elastic recoil of the aorta (= **Windkessel effect**) during ventricular diastole. The difference between the systolic and diastolic B.P. is called the **pulse pressure**. It normally averages 40 mmHg and its magnitude is determined by the **stroke volume**, the **speed by which the stroke volume is ejected** and the **compliance (distensibility)** of the arteries (page 40).

The mean arterial blood pressure

This is the average arterial pressure during the cardiac cycle. It is the pressure responsible for tissue perfusion with blood, and all pressure regulatory mechanisms cooperate to keep it constant. It is normally less than 100 mmHg (the arithmetic mean of $120 + 80$) *because the arterial pressure remains closer to the diastolic pressure for a longer part of the cardiac cycle than the systolic pressure* (the diastolic period occupies about 2/3 of the cardiac cycle). The following formula is generally used to calculate the mean arterial blood pressure :

$$\text{Mean B.P.} = \text{Diastolic B.P.} + \frac{1}{3} \text{ pulse pressure} = 80 + 13 = 93 \text{ mmHg.}$$

MEASUREMENT OF THE ARTERIAL B.P.

The arterial B.P. should be measured in an artery placed at the level of the heart to eliminate the effect of gravity. Therefore, it is usually measured in the **brachial artery** while the person is in the **recumbent position**, and one of the following methods can be used :

(1) **Direct measurement** : This is performed by inserting a **cannula** into the artery and connecting it to a manometer. *However, this method is used only in special cases.*

(2) **Indirect measurement** : This is performed *routinely* using an apparatus called the **sphygmomanometer** (refer to the practical book), which can measure the arterial B.P. by both a **palpatory method** (for *rough measurement of the systolic pressure*) and an **auscultatory method** (for *accurate measurement of both the systolic and diastolic pressures*).

PHYSIOLOGICAL CHANGES OF THE ARTERIAL B.P.

The level of the arterial B.P. is normally changed by the following factors :

- (1) **Site of measurement** : It is higher in the lower than in the upper limbs.
- (2) **Age** : It is low at birth (about 70-80 / 40-50 mmHg) then it rises till about 120 / 80 mmHg at the age of 20 years. After that it gradually increases becoming about 150 / 90 mmHg after the age of 60 years.
- (3) **Sex** : It is generally slightly higher in adult males than in females.
- (4) **Body built (constitution)** : It is usually high in obese persons.
- (5) **Race** : It is often high in western countries.
- (6) **Diurnal variation** : It is low in the morning and high in the afternoon.
- (7) **Meals** : It increases slightly after meals.
- (8) **Exercise** : It markedly increases during exercise (specially the systolic).
- (9) **Emotions** : It increases in most emotions (specially the systolic).
- (10) **Intercourse** : It is often increased during intercourse.
- (11) **Sleep** : It is often slightly decreased during quiet sleep.
- (12) **Temperature** : In hot environments, the systolic pressure increases due to tachycardia, but the diastolic pressure may fall due to cutaneous V.D..
- (13) **Gravity** : On standing, the force of gravity increases the mean arterial pressure below the heart level by about 0.77 mmHg / cm.
- (14) **Respiration** : The arterial B.P. shows rhythmic fluctuations during the respiratory cycle called *Traube-Hering waves*. It increases during inspiration (due to the increase in VR and CO) and decreases during expiration.

FACTORS THAT DETERMINE & MAINTAIN THE ARTERIAL B.P.

Many factors determine and maintain (and also affect) the level of the arterial B.P. The main determinants of the arterial B.P. are the **cardiac output (CO)** and the **resistance to blood flow** offered by the vascular system (specially the *peripheral resistance in the arterioles*). Therefore, the **mean systemic arterial B.P. = CO x peripheral resistance** (page 94). In addition, the *elasticity (compliance or distensibility) of the aorta* also contributes.

(1) CARDIAC OUTPUT (CO)

The arterial B.P. is directly proportionate to the CO [which equals the product of the stroke volume (SV) x heart rate (HR)]. With a constant HR, changes in the *SV affect mainly the systolic pressure* (an increase in the SV increases the systolic pressure and vice versa). On the other hand, with a constant SV, *changes in the HR affect mainly the diastolic pressure* (an increase in the HR increases the diastolic pressure and vice versa).

Effect of the blood volume and vascular capacitance

These affect the arterial B.P. through changing the mean circulatory pressure (MCP), the venous return (VR) and the SV. An increase of the

blood volume or a decrease of the vascular resistance (by venoconstriction) would increase the MCP, so the VR is increased (page 81) leading to an increase of the EDV and SV, thus the systolic pressure rises. Conversely, the systolic pressure falls in opposite conditions.

(2) PERIPHERAL RESISTANCE (PR)

The PR is essential for maintenance of the arterial blood pressure particularly the **diastolic pressure**. It is determined by: (a) The radius (or diameter) of the vessel (b) Blood viscosity (c) The length of the vessel. However, normally the *arteriolar diameter is the main determinant factor* because the other 2 factors are normally kept constant (page 94).

(3) ELASTICITY (COMPLIANCE) OF THE AORTA

Part of the pumping energy of the heart is expended in distention of the aorta. This energy is released during cardiac diastole causing **elastic recoil of the aortic wall**. Such effect is essential for maintenance of a relatively **high diastolic B.P.** and is called the **Windkessel effect**.

In addition, the aortic elasticity prevents excessive rise of the systolic B.P., and the effects of its loss (in arteriosclerosis) are (a) Rise of the systolic pressure and fall of the diastolic pressure leading to *increase of the pulse pressure* (page 40) (b) The blood flow to the tissues becomes *almost only during systoles* (page 33) (c) The *velocity of pulse wave transmission is increased* (page 39).

THE BARORECEPTORS (PRESSORECEPTORS)

These are stretch receptors that provide the nervous system with information about the *level of the arterial blood pressure*. They are located in the *walls of certain blood vessels as well as the heart*, and include the following

(1) **The arterial baroreceptors** : These are located in the wall of almost *every large artery in the thoracic and neck regions*, but particularly in the walls of the *carotid sinuses and aortic arch* (page 71).

(2) **The cardiopulmonary baroreceptors** : These are located in the walls of *both atria, the left ventricle and the pulmonary vessels*. Their stimulation leads to the *same effects produced by stimulation of the arterial baroreceptors* (temporary apnea, bradycardia, generalized V.D. and hypotension).

THE ARTERIAL BARORECEPTORS

These are responsible for production of the *cardiac vagal tone* (page 70) and *play a major role in short-term regulation of the arterial blood pressure* (see below). They provide signals to the vasomotor centre *about both the mean arterial pressure and the pulse pressure*. Signals from the carotid sinus baroreceptors provide information regarding the arterial pressure *within the range of about 50 – 180 mmHg* and are transmitted by a branch of the glossopharyngeal nerve called the *sinus (or hering) nerve* (page 71). On the other hand, the *aortic baroreceptors operate at pressure levels about 30 mmHg higher than the carotid receptors* and their signals are transmitted by a branch of the vagus nerve called the *aortic nerve* (page 71).

REGULATION (CONTROL) OF THE ARTERIAL B.P.

Whenever the arterial blood pressure is altered, it will be restored to the normal level by **short and long term mechanisms**.

(I) SHORT-TERM MECHANISMS

These are **rapidly acting pressure control mechanisms**. They constitute the *first line of defense* against alterations of the arterial B.P. (so they are *life saving*). They can be divided into (A) Mechanisms that start acting within a *few seconds* (B) Mechanisms that start acting within a *few minutes* (these can be called **intermediate-term pressure control mechanisms**).

(A) Mechanisms that start acting within a few seconds

These are concerned with *moment to moment control* of the arterial blood pressure, and are mostly *nervous reflexes*. They become *fully active within a minute* and include the following :

(1) The baroreceptor reflex (buffer function of baroreceptors)

The *arterial baroreceptors* and their connections constitute a control system that opposes changes in the arterial blood pressure, so this system is called the **pressure buffer system**, and the sinus and aortic nerves are called the **buffer nerves**. These receptors *monitor and buffer changes in the arterial blood pressure* by the following mechanism :

(a) When the arterial blood pressure increases, the arterial walls are stretched and the baroreceptors are stimulated resulting in an increase of their discharge rate. Signals initiated from these receptors are conducted by the buffer nerves to the vasomotor centre where they lead to stimulation of the CIC and VDC and inhibition of the VCC. Such responses lead to reduction of the arterial blood pressure by **decreasing** (1) The peripheral resistance (through producing V.D. in both the arterioles and venules) (2) The CO (through decreasing the heart rate and cardiac contractility) and (3) Catecholamine secretion from the adrenal medullae.

(b) When the arterial blood pressure decreases (e.g. due to hemorrhage), the discharge rate from the baroreceptors is decreased. This *releases the VCC from their inhibitory effect and decreases the activity of the CIC and VDC*. Accordingly, the cardiac vagal tone is decreased and the sympathetic discharge to the heart and blood vessels is increased (and catecholamines are released from the adrenal medullae). These effects increase the heart rate and contractility (so the cardiac output increases) and lead to arteriolar V.C. (which increases the peripheral resistance) as well as venous V.C. (which increases the venous tone and venous return). All these responses help elevation of the arterial blood pressure toward the normal level.

Role of the arterial baroreceptors on changing the body posture

A sudden change from the recumbent to the upright posture tends to decrease the arterial blood pressure due to reduction of the VR and CO as a result of pooling of blood in the lower limbs by the **effect of gravity** (page 86). However, this *decreases the discharge from the baroreceptors*, leading to *increased sympathetic discharge to the heart and blood vessels* and the *resulting tachycardia, increased cardiac contractility and arteriolar and venous V.C. prevent drop of the arterial blood pressure* (page 126).

IMPORTANT REMARKS ON THE BARORECEPTORS

****** The arterial baroreceptors are not important in long term regulation of the arterial blood pressure because they become *reset (adapted) within 1 -2 days*

****** The *low pressure receptors in the atria and pulmonary vessels* are stretch receptors similar to the arterial baroreceptors, but they *respond to lower pressures*. In fact, they are **volume receptors** the primary function of which is to *regulate the blood volume* but while doing so, *they also minimize changes in the arterial blood pressure* e.g. an increase in the blood volume tends to increase the arterial blood pressure. However, stimulation of the volume receptors leads to *generalized arteriolar and venous V.D. (but with tachycardia rather than bradycardia, page 74)*. In addition, several effects

known as the **volume reflex** are produced in the **kidneys**. These include (a) Increased glomerular filtration (due to V.D. of the glomerular capillaries) (b) Increased water excretion by the kidneys due to reflex inhibition of secretion of the antidiuretic hormone (c) Increased renal Na^+ excretion due to secretion of ANP (= atrial natriuretic peptide) from the distended atrial walls. *All these effects decrease the blood volume and together with the generalized V.D. they also minimize elevation of the arterial blood pressure.*

**** There are intra-renal baroreceptors** (the juxtaglomerular cells in the walls of the afferent renal arterioles) which respond to a decrease in the arterial blood pressure (or renal ischemia) by secreting **renin** (see below).

**** Cutting of the sinus nerves** stops the signals from the arterial baroreceptors and is interpreted as a drop in the mean arterial pressure. Thus, generalized V.C. together with increased heart rate and contractility occur resulting in *rise of the arterial blood pressure*. On the other hand, subsequent stimulation of the central end of the cut sinus nerves is interpreted as a rise of the arterial blood pressure and this causes generalized V.D. together with decreased heart rate and contractility, which leads to drop of the arterial pressure.

**** Occlusion of the common carotid arteries decreases the pressure in the carotid sinuses.** This leads to generalized V.C. and increased heart rate and contractility, which results in *rise of the arterial blood pressure*.

The abdominal compression reflex : Whenever the baroreceptor (or chemoreceptor) reflex is initiated (in cases of drop of the arterial blood pressure), stimulation of the VCC is associated with excitation of the medullary reticular formation and this discharges signals via somatic nerves to the abdominal muscles leading to their contraction. This is an important mechanism to increase the arterial blood pressure because it increases the intraabdominal pressure which compresses the venous reservoirs of the abdomen resulting in an increase of the venous return and cardiac output

(2) The chemoreceptor reflex

The receptors of this reflex are located in the **carotid and aortic bodies**. These are stimulated when the arterial blood pressure is decreased below 80 mmHg (mainly as a result of local decrease in PO_2 which occurs secondary to ischemia). In this case, they discharge signals in the **buffer nerves** that stimulate the VCC, which leads to elevation of the arterial blood pressure. However, the chemoreceptors play a much more important role in the control of respiration than in regulation of the arterial blood pressure.

(3) The CNS ischemic response

In cases of severe reduction of the mean arterial blood pressure (below 50 or 60 mmHg), *brain ischemia occurs*, and the resulting *increase in PCO_2 and hypoxia* stimulate the vasomotor centre, resulting in rise of the arterial blood pressure that is associated with **bradycardia** (due to either simultaneous increase in vagal discharge or secondary to stimulation of the arterial baroreceptors). Such response is *not a normal mechanism* for arterial blood pressure regulation because it *becomes significant only at very low levels of the arterial blood pressure*. It operates only as an *emergency pressure control system* when the cerebral blood flow decreases to fatal levels.

Cushing reflex (or reaction) : *Rise of the intracranial pressure (i.e. CSF pressure) results in rise of the arterial blood pressure and bradycardia.* The rise of the intracranial pressure leads to *brain ischemia* (due to compression of the cerebral blood vessels), and the resulting *hypoxia and increase in PCO_2* stimulate the vasomotor centre, leading to rise of the arterial blood pressure (which increases the cerebral blood flow) that is associated with **bradycardia** as occurs in the CNS ischemic response.

(B) Mechanisms that start acting within a few minutes

These are **autoregulatory intermediate-term mechanisms** that are initiated within 20-30 minutes after alteration of the arterial blood pressure, become maximal after several hours (during which the nervous mechanisms almost disappear completely) and they last for a few days. They include :

(1) Capillary fluid shift mechanism : When the arterial blood pressure is altered, the exchange of fluids in the capillaries contributes to its return to the normal level e.g. elevation of the arterial blood pressure usually increases the capillary hydrostatic pressure, and this increases fluid filtration into the tissue spaces, thus the blood volume is decreased leading to reduction of the arterial blood pressure toward the normal level. The opposite occurs when the arterial blood pressure is decreased.

(2) Stress relaxation mechanism : Changes in the arterial blood pressure gradually causes the blood vessels to attain new sizes that accommodate the present amounts of blood e.g. rise of the arterial blood pressure following massive blood transfusion initially stretches the arteries and increases the tension in their walls. However, within a few minutes to an hour the arteries relax and the tension in their walls decreases. This is called **stress relaxation of the arteries**, and it helps lowering of the arterial blood pressure. When the arterial blood pressure falls, it can be elevated by an opposite mechanism (= **reverse stress relaxation**).

(3) Renin-angiotensin V.C. mechanism : A fall of the arterial blood pressure leads to renal ischemia. This stimulates secretion of an enzyme called **renin** from the juxtaglomerular cells of the kidney, which acts on a plasma alpha 2 globulin called **angiotensinogen** (a polypeptide synthesized by the liver) forming a decapeptide called **angiotensin I**. An enzyme called *angiotensin-converting enzyme* converts angiotensin I into an octapeptide called **angiotensin II** (*mostly in the lungs*), which has a potent V.C. effect that increases the arterial blood pressure. Angiotensin II also stimulates secretion of a hormone called **aldosterone** from the adrenal cortex, which is involved in long-term regulation of the arterial blood pressure (see next).

(II) LONG-TERM MECHANISMS

These mechanisms control the arterial blood pressure over long periods (months and years) by a **renal body fluid mechanism** i.e. by adjusting the body fluids and blood volume through modifying the excretion of water and salt by the **kidneys**. This occurs by changes in *the rates of glomerular filtration and secretion of the aldosterone hormone* as follows :

(1) A fall of the arterial blood pressure leads to (a) Reduction of the glomerular filtration rate (which promotes water and salt retention in the body) (b) Secretion of **renin**, which stimulates aldosterone secretion from the adrenal cortex through formation of angiotensin II (see above). This hormone increases Na^+ reabsorption from the renal tubules together with water, and such effect together with reduction of the glomerular filtration rate increases the body fluids and blood volume, which elevates the arterial blood pressure toward the normal level.

(2) A rise of the arterial blood pressure increases glomerular filtration, producing **pressure diuresis** (which leads to loss of water and salt in the urine). At the same time, renin secretion is inhibited, so aldosterone secretion is decreased, leading to loss of Na^+ and water in the urine. This effect together with pressure diuresis decreases the body fluids and blood volume, which reduces the arterial blood pressure toward the normal level.

Hormones involved in regulation of the arterial blood pressure

(1) **Catecholamines :** These are secreted by the adrenal medullae whenever the sympathetic system is activated secondary to stimulation of the VCC and they augment its effects on the heart and blood vessels to elevate the arterial blood pressure. They are *involved only in short-term regulation* of the arterial blood pressure because their effects last for only 2 - 3 minutes.

(2) **Aldosterone:** This is involved in *intermediate and long-term regulation* of the arterial blood pressure (see above).

(3) **ADH (= antidiuretic hormone or vasopressin)** : Through its action on the kidneys, ADH *promotes water retention in the body*. It also exerts a *considerable V.C. effect* and is important for elevation of the arterial blood pressure when it is severely decreased (e.g. in acute hemorrhage). However, it is *not involved in moment to moment regulation of the arterial pressure*.

Major differences between the short and long term mechanisms involved in regulation of the arterial blood pressure

(1) The short term mechanisms are rapidly acting (within seconds or minutes) and are concerned with correction of acute alterations of the arterial blood pressure as well as its moment to moment control. On the other hand, the long term mechanisms are slowly acting and are concerned with maintenance of the arterial blood pressure constant over long periods.

(2) The short term mechanisms lose their efficiency rapidly and almost disappear completely within a few days. On the other hand, the long term mechanisms become steadily greater with time.

(3) The short term mechanisms cannot completely bring an altered arterial blood pressure back to the normal level. On the other hand, the long term mechanisms are highly potent and can bring an altered arterial blood pressure back to the normal level but at a longer time.

EXPERIMENTAL HYPERTENSION (INDUCTION OF HYPERTENSION)

Hypertension can be artificially-produced in experimental animals (for research purposes) by one of the following methods :

(1) Producing **renal ischemia** (by constricting the renal arteries or the aorta just above the origin of the renal arteries). Such **renal hypertension** is partially caused by *salt and water retention* (due to poor renal blood flow) but it is mainly the result of **renin** secretion, which leads to formation of angiotensin II, the actions of which increase the arterial blood pressure (see below).

(2) **Partial nephrectomy with a high salt intake** : This produces hypertension due to decreased renal ability to excrete the excess salt.

(3) **Denervation of the arterial baroreceptors** : This leads to tachycardia and V.C., resulting in what is known as **neurogenic hypertension**.

(4) Ligation of the major cerebral arteries (**cerebral ischemia**) : This increases the arterial blood pressure by the **CNS ischemic response** (page 105).

(5) Exposing the animal to **repeated loud noises** : This increases the arterial blood pressure due to excitation of the vasomotor centre by cortical impulses

(6) Administration of large doses of mineralocorticoids e.g. **aldosterone**.

(7) Production of strains of animals that easily develop hypertension either spontaneously or when fed diets rich in salt (**genetic hypertension**).

ACTIONS OF ANGIOTENSIN II

- (1) Generalized potent V.C. (4-8 times as active as norepinephrine).
- (2) Facilitation of norepinephrine release from the sympathetic nerves.
- (3) Stimulation of aldosterone secretion from the adrenal cortex.
- (4) Decreasing glomerular filtration (by causing contraction of the mesangial cells in the renal glomeruli) and *increasing Na^+ reabsorption by a direct action on the proximal tubules of the renal nephrons* (refer to kidney).
- (5) Excitation of certain structures located above the brain stem in relation to the hypothalamus known as the **circumventricular organs** (page 134), which lead to (a) *Release of the antidiuretic hormone (helps water retention in the body)* (b) *Thirst (increases water intake)* (c) *Secretion of ACTH* (a hormone that stimulates secretion of hormones from the adrenal cortex).

Angiotensins III and IV

An aminopeptidase removes one amino acid from the angiotensin II molecule and the resulting **heptapeptide is called angiotensin III**. This has 40 % only of the pressor activity of angiotensin II but 100 % of its aldosterone-stimulating activity. Subsequent removal of another amino acid produces the **hexapeptide called angiotensin IV**, which is said to have some activity.

HYPERTENSION (HIGH ARTERIAL BLOOD PRESSURE)

This serious disease is diagnosed if the *mean arterial blood pressure of a resting adult person exceeds 110 mmHg* (which occurs when the diastolic pressure is greater than 90 mmHg and the systolic pressure is greater than 140 mmHg). *Its severity is evaluated on the basis of the diastolic pressure* (up to 100-105 mmHg is mild, between 105 and 115 mmHg is moderate, and more than 115 mmHg is severe). Both systolic and diastolic pressures are usually elevated, but there are some cases of isolated increase in either.

Although hypertension can result from an increase in the cardiac output, the main cause in most cases is *an increase in the total peripheral resistance*. Generally, there are 2 main types of hypertension :

(A) Primary (or essential) hypertension

This constitutes about 90 % of cases. It is associated with narrowing of the resistance vessels (i.e. arterioles) of unknown cause. It is frequently inherited but social and environmental factors are also involved. In chronic cases, the baroreceptor reflex regulatory mechanism (page 102) is reset to a *higher set point than normal* (i.e. it acts to maintain the elevated pressure).

(B) Secondary (or symptomatic) hypertension

This is an elevation of the arterial blood pressure as a result of other diseases (i.e. the cause is known), and it accounts for about 10 % of cases. The common diseases that cause hypertension include the following :

(1) Renal diseases associated with renal ischemia (and also tumours of juxtaglomerular apparatus). In these cases, hypertension occurs mainly due to activation of the *renin-angiotensin system* (= *renal or Goldblatt hypertension*).

(2) *Pheochromocytoma* (= tumour of the adrenal medulla) : This causes hypertension due to excessive secretion of catecholamines by the tumour.

(3) *Cushing's and Conn's syndromes* : These cause hypertension due to excessive secretion of hormones from the adrenal cortex (glucocorticoids in the former and aldosterone in the latter), and these hormones promote Na^+ and water retention in the body which elevates the arterial blood pressure.

(4) *Toxemia of pregnancy* : Hypertension in this case is believed to be due to release of toxic substances from the placenta (? as a result of ischemia) that cause generalized dysfunction of the vascular endothelial cells. This decreases the release of NO (and other vasodilator substances) from the endothelial cells, which leads to generalized V.C. resulting in hypertension (due to increased peripheral resistance and decreased glomerular filtration rate).

(5) *Polycythemia* : This increases the blood viscosity, so the peripheral resistance is increased, resulting in elevation of the arterial blood pressure.

(6) *Prolonged intake of contraceptive pills* : This produces hypertension in some women (= *pill hypertension*) due to an increase of the angiotensinogen blood level (the production of which is stimulated by the estrogen hormone).

(7) *Aortic coarctation* : This is congenital narrowing of a segment of the thoracic aorta. The arterial blood pressure is markedly elevated in the upper parts of the body. However, it is usually *not decreased in the lower parts* (and may even be slightly increased) because the resulting renal ischemia activates the renin-angiotensin system (which prevents drop of the arterial blood pressure in the lower parts of the body).

Complications of hypertension

(1) Excess work load on the heart. Left ventricular hypertrophy occurs in chronic cases (in which it often terminates by heart failure).

(2) Degenerative changes and atherosclerosis in the blood vessels as a result of the excessive pressure. This predisposes to :

(a) Thrombosis in the cerebral vessels or cerebral hemorrhage (clinically called a *cerebral stroke*)

(b) Thrombosis in the coronary vessels (coronary heart disease) which often terminates by a *heart attack* (myocardial infarction).

(c) Damage of the kidneys, which often terminates by *renal failure*.

**** Malignant hypertension** is a term that refers to severe cases of hypertension associated with extensive necrotic vascular lesions and progressive renal failure without an obvious cause. Without treatment, it results in rapid deterioration of the patient and death occurs in less than 2 years.

Physiological basis of treatment of hypertension

Hypertension definitely *shortens life expectancy*. Secondary hypertension can be prevented by treating the underlying cause, while primary hypertension can be treated by *salt restriction* and the following *hypotensive drugs* :

(1) *Drugs that decrease the peripheral resistance* : These include vasodilator drugs (that directly relax smooth muscle) as well as sympatholytic drugs (e.g. reserpine and aldomet). These drugs also improve the renal blood flow.

(2) *Drugs that decrease the strength of cardiac contractility and heart rate* (to decrease the cardiac output). These are mostly beta blockers e.g. atenolol.

(3) *Drugs that prevent formation of angiotensin II* specially the *angiotensin converting enzyme (ACE) inhibitors* e.g. captopril.

(4) *Diuretic and natriuretic drugs* : These drugs increase Na^+ and water excretion by the renal tubules (see in kidney) thus reducing the blood volume.

HYPOTENSION

This is a state of low arterial blood pressure less than 100 / 60 mmHg. It is due to a decrease of either the peripheral resistance or the cardiac output (or rarely both), and it may be primary or secondary. The primary type has no obvious causes and occurs specially in young individuals who have asthenic (weak) slender bodies. On the other hand, the secondary type occurs as a result of disease or other conditions, which include the following :

(1) Cardiovascular diseases associated with low cardiac output e.g. mitral or aortic stenosis.

(2) Certain endocrine diseases e.g. hypothyroidism and adrenocortical hypofunction (= Addison's disease).

(3) Hypovolemia e.g. due to acute severe hemorrhage or loss of large quantities of extracellular fluid (as occurs in severe diarrhea and vomiting).

(4) Excessive release of vasodilator substances (as occurs in severe infections and allergy).

(5) Loss of the sympathetic V.C. tone (the vasomotor tone). This may occur in some emotions as a result of impulses discharged from certain areas in the cerebral cortex that depress the VCC. It leads to fainting known as **the vasovagal syncope** due to cerebral ischemia (page 150) that can be relieved by lying down (which increases the venous return and cardiac output).

In general, hypotension can be treated by giving drugs that induce V.C. and by treatment of the cause (in the secondary type).

CHAPTER 10

REGULATION OF THE ARTERIOLAR DIAMETER

The arteriolar diameter *determines the peripheral resistance as well as the blood flow to the tissues*. It is regulated by **local and systemic factors**.

(A) Local regulation of the arteriolar diameter

This is concerned with control of the **local blood flow rate in the tissues** and is produced by the effects of the following factors :

(1) **Local O₂ tension** : A local decrease in PO₂ leads to arteriolar V.D. directly (which increases the local blood flow rate in active tissues).

(2) **Metabolites** : Most metabolites formed during activity cause arteriolar V.D. and relaxation of the precapillary sphincters. These metabolites include CO₂, K⁺, H⁺, histamine, lactic acid, ADP and adenosine (the latter is the most potent, and is formed specially in the cardiac muscle).

(3) **Local temperature** : Rise of temperature in active tissues (by the heat of metabolism) causes arteriolar V.D. that increases the blood flow.

(4) **Autoregulation** : This is the ability to maintain a constant blood flow in spite of changes in the perfusion pressure. It is well developed in the kidneys, and is explained by 2 theories :

(a) **Metabolic theory** : This is the most accepted theory. As the perfusion pressure is decreased, the blood flow is reduced leading to local O₂ lack and accumulation of metabolites. Both effects lead to V.D., thus the blood flow is increased and is kept relatively constant. Opposite effects occur when the perfusion pressure is increased (the metabolites are washed and V.C. occurs, so the blood flow is reduced and is kept relatively constant).

(b) **Myogenic theory** : As the perfusion pressure increases, the arterioles distend and in response, their smooth muscle fibres contract, so their diameters are decreased and the blood flow is not much increased.

(5) **Locally-released (paracrine) arteriolar regulators** : The following substances are released locally at tissues and affect the arteriolar diameter :

a- **Serotonin and thromboxane A₂** (V.C. substances released from platelets)

b- **Prostaglandin I₂ (prostacyclin)**, a V.D. substance formed by the endothelial cells that line the blood vessels (*the vascular endothelium*).

c- **Endothelin I**, a potent V.C. peptide formed by the *vascular endothelium*.

d- **Endothelium-Derived Relaxing Factor (EDRF)**. This is a powerful V.D. substance secreted by the *vascular endothelium*, and chemically it is **nitric oxide (NO)**. Many V.D. substances act through stimulating formation of the EDRF (e.g. acetylcholine, bradykinin, VIP and substance P).

****** There are 3 types of endothelins (ET). They are produced primarily in the kidneys, brain and GIT, in which ET-1 exerts a potent V.C. effect (see above), while ET-2 and ET-3 exert developmental effects.

****** NO is synthesized from arginine by activity of NO-synthase enzyme. It *activates guanylyl cyclase*, which acts on GMP and the formed **c-GMP** relaxes the vascular smooth muscle leading to V.D. NO is also important for brain functions as well as the cytotoxic activity of macrophages. Furthermore, penile erection induced by parasympathetic stimulation is believed to be produced as a result of the V.D. effect of locally formed NO.

FUNCTIONS OF THE VASCULAR ENDOTHELIUM

In addition to preventing intravascular clotting, the vascular endothelium releases (1) EDRF (NO) (2) Endothelins (3) Prostacyclin and ? thromboxane A_2 (4) Thrombomodulin (5) Von-Willebrand factor (6) Platelet Derived Growth Factor (7) Some interleukins and colony-stimulating factors (8) VEGF (vascular endothelial growth factor) (9) Kinins (see below).

Active and reactive hyperemia

Active hyperemia is the *increase in the local blood flow that occurs in an active organ* (e.g. a skeletal muscle during exercise). It is due to V.D. of the arterioles and relaxation of the precapillary sphincters that occur secondary to the local decrease of PO_2 and the release of V.D. metabolites.

On the other hand, reactive hyperemia is the *increase in the blood flow to an organ that occurs after temporary blockage of its blood supply*. Such increase in blood flow occurs by the *same mechanisms as in active hyperemia specially the local decrease of PO_2* . It can be demonstrated by the **plethysmograph** (page 98) as follows : The arterial blood supply to the forearm is occluded (by raising the pressure in a sphygmomanometer cuff above the systolic pressure) for a few minutes, then the pressure is released. An increase in the volume of the forearm will occur due to an increase in the blood flow, and is often associated with **ischemic pain** (refer to C.N.S.).

(B) Systemic regulation of the arteriolar diameter

This is concerned with control of the **peripheral resistance allover the body** so as to *maintain a constant arterial blood pressure*. It includes **chemical and nervous regulation**.

(I) CHEMICAL REGULATION

The main circulating V.C. substances include catecholamines, vasopressin (= antidiuretic hormone) and angiotensin II. *The main circulating V.D. substances* include ANP (Atrial Natriuretic Peptide), VIP (Vasoactive Inhibitory Polypeptide), histamine, substance P and kinins (see next).

KININS

These are potent V.D. peptides, of which there are 2 types in the body called **bradykinin** and **kalidin**. They are formed from 2 precursor proteins called *high and low molecular weight kininogens* by activity of the protease enzyme **kallikrein**. (which is formed from prekallikrein by active factor XII)

The actions of kinins are similar to those of histamine, and include :

- (1) Contraction of visceral smooth muscle
- (2) Relaxation of vascular smooth muscle (via NO), leading to V.D.
- (3) Increasing the capillary permeability
- (4) Attraction of leukocytes
- (5) Stimulation of pain receptors.

Kinins are formed during activity of the salivary, sweat and exocrine pancreatic glands, causing V.D. and increase of the blood flow in these glands.

** 2 enzymes called **kininase I and II** inactivate kinins [note that *kininase II is itself the angiotensin converting enzyme (ACE)*].

(III) NERVOUS REGULATION

Vasoconstrictor (V.C.) nerves

These are the **sympathetic nerves** all over the body except some sympathetic V.D. fibres (see below). The sympathetic discharge is controlled by descending signals from the vasomotor centre via the reticulospinal tract, and during rest there is a basal tonic discharge in the sympathetic nerves known as the **V.C. or vasomotor tone**, which causes partial V.C. in the arterioles all over the body. This produces *peripheral resistance* to blood flow, which is essential to maintain the arterial blood pressure (page 101).

Vasodilator (V.D.) nerves

The V.D. nerves in the body include the following :

- (1) *All parasympathetic postganglionic nerve fibres.*
- (2) *The sympathetic V.D. fibres*, which innervate the coronary vessels and some visceral blood vessels, as well as the skeletal muscle vessels via the *sympathetic V.D. system* (refer to the autonomic nervous system).
- (3) *The antidromic somatic V.D. fibres* : Excitation of the cutaneous pain receptors is frequently associated with V.D. of arterioles. The signals generated at the skin receptors are transmitted by an afferent nerve to the nervous system, then they return *antidromically* (i.e. in the opposite direction) via a branch of the afferent nerve and terminate at adjacent arterioles (figure 60) causing V.D. by releasing **substance P**. Such effect is known as **flare**, and is well apparent in the **triple response** (page 121). This V.D. mechanism is called a **local axon reflex** because the nervous system is not involved (so it persists after section of the afferent nerves central to the dorsal root ganglia).

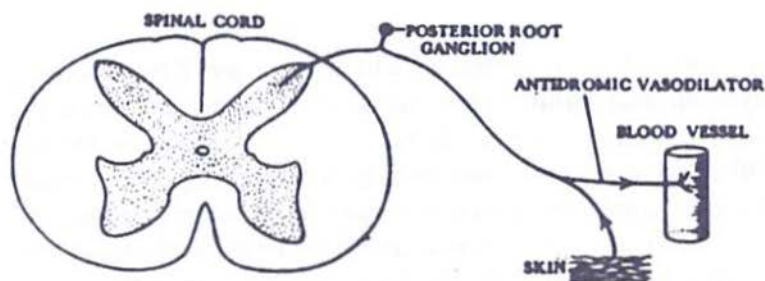


Figure 60 : The antidromic somatic vasodilator fibres.

Factors that affect the vasomotor centre (VMC)

(A) Nervous factors

- (1) Impulses from the baroreceptors inhibit the VCC and stimulate the CIC.
- (2) Impulses from the chemoreceptors stimulate the VCC.
- (3) Cortical impulses commonly stimulate the VCC in cases of stress and emotional excitement, increasing the arterial blood pressure. However, hypotension and **vasovagal syncope** may occur in some emotions (page 110).
- (4) Impulses from the hypothalamus may stimulate the VCC (e.g. during exposure to cold) or the VDC (e.g. during exposure to heat).
- (5) Impulses from the respiratory centre stimulate the VCC, elevating the arterial blood pressure during late inspiration and early expiration.
- (6) Somatic signals from contracting muscles and in case of moderate pain stimulate the VCC by a **somatosympathetic reflex**, causing rise of the arterial pressure (but severe pain may inhibit the VCC, leading to hypotension).

(B) Chemical factors

A decrease in the arterial PO_2 stimulates the VCC directly and through stimulating the chemoreceptors, causing rise of the arterial blood pressure. An increase in the arterial PCO_2 or H^+ also stimulate the VCC (the former directly and the latter through stimulating the chemoreceptors). *It is to be noted that local decrease of PO_2 in the tissues or increase of PCO_2 or H^+ leads to arteriolar V.D.* (page 111).

(C) Physical factors

Heat causes direct V.D. of the arterioles while cold produces direct V.C. besides the role of the hypothalamus. *Freezing produces V.C. that is followed by V.D.* which occurs as a result of accumulation of V.D. metabolites (due to the decreased blood flow) and release of histamine from the damaged tissues (so the nose, finger tips and ear lobes appear red in winter)

The cold pressor test

This test demonstrates the VC effect of cold impulses (see above). The arterial pressure is measured at one limb, then the other limb is immersed in ice water for one minute, and the pressure is re-measured at the first limb. It increases by 5-10 mmHg in normal persons, but in hypertensive patients and individuals with autonomic hyper-reactivity (i.e. liable to develop hypertension), the arterial pressure will increase by 25 mmHg or more.

Effects of bilateral vagotomy on the arterial pressure

Afferent vagal nerves can produce both VD (by impulses from the baroreceptors in the aortic arch) as well as VC (by impulses from the chemoreceptors in the aortic bodies), and *during rest the VD effect predominates*. Bilateral vagotomy affects the arterial blood pressure as follows :

(1) If the arterial blood pressure was high or normal, the VD vagal effect predominates, and bilateral vagotomy in such conditions abolishes this effect, leading to a *further increase of the arterial blood pressure*.

(2) If the arterial blood pressure was low, the VC vagal effect predominates, and vagotomy in such condition abolishes this effect, leading to a *further decrease of the arterial blood pressure*.

Arterial occlusion

This may occur *as a result of either a mechanical obstruction or vascular spasm (VC)*. The cause can be detected by *plethysmography* (page 98) as follows : The organ at which the artery is occluded is warmed (or a sympatholytic drug is given) and the volume of the organ is measured. Its volume would increase if the occlusion was due to a vascular spasm (because of the resulting VD), but it would not change if the occlusion was due to a mechanical obstruction.

Sympathectomy

This is an operation that is performed to induce V.D. in an organ (to increase its blood flow). The *section should be in the preganglionic fibres* because if it was in the postganglionic fibres, the operation may fail since arteriolar VC may occur again as a result of hypersensitivity to the circulating catecholamines (according to the *law of denervation*).

CHAPTER 11

THE CAPILLARY (MICRO) CIRCULATION AND LYMPH CIRCULATION & EDEMA

STRUCTURE OF THE MICROCIRCULATION

The arterioles divide into *metarterioles*, and the capillaries arise from both (figure 61). The metarterioles are directly connected to the venules by *thoroughfare vessels*, and the capillaries drain in these vessels as well as in the venules. The openings of the capillaries are surrounded by smooth muscles called *precapillary sphincters* which respond to various stimuli.

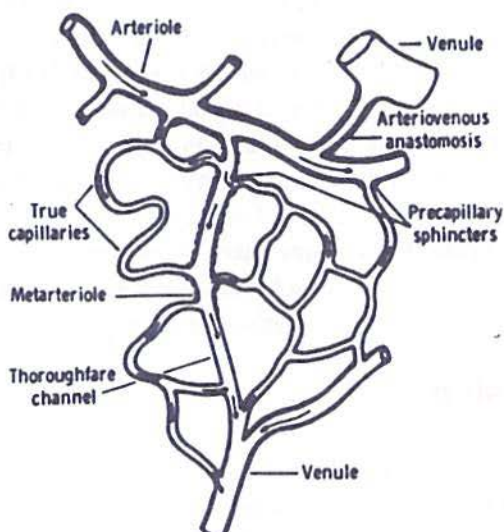


Figure 61 : Structure of the microcirculation.

There are about 40 billion capillaries in the body of an adult with a total surface area exceeding 6300 m^2 , and normally only 10 billions are open at a time. The cross sectional area of *all open capillaries* is about 4500 cm^2 with an average velocity of blood flow *would be* 0.2 mm / second (page 95). Their walls are about one micron thick, and each is about 0.7 mm long.

Capillaries are generally made up of a single layer of endothelial cells surrounded by a basement membrane and certain cells called *pericytes*. They are commonly divided into 3 main types (1) **Continuous capillaries** (in the muscles and brain) (2) **Fenestrated capillaries** (in the kidneys, intestinal villi and most endocrine glands) (3) **Sinusoidal capillaries** (in the liver, spleen and bone marrow).

****** Since the capillary walls contain no smooth muscle fibres, they are passive (i.e. they do not contract or relax) and their dilatation or constriction depends on the state of the precapillary sphincters (their contraction leads to capillary constriction while their relaxation leads to capillary dilatation).

VASOMOTION

Vasomotion means intermittent opening and closure of the capillaries. It is a normal phenomenon that occurs every few seconds to few minutes as a result of rhythmic contraction and relaxation of the metarterioles and precapillary sphincters. It causes intermittent blood flow to the tissues, and its rate is controlled mainly by the oxygen level in the tissues (O_2 lack prolongs the capillary opening periods and shortens their closure periods, and vice versa).

FUNCTIONS OF CAPILLARIES

The capillaries contain only about **5 % of the blood volume** at a time and they constitute the *site at which the exchange of various substances between the blood and interstitial fluid occurs*. It is across the capillary walls that O_2 and various nutrients enter the interstitial fluid, while CO_2 and various waste products enter the blood.

FACTORS THAT AFFECT THE CAPILLARY PRESSURE (CP)

The CP is normally averages **32-35 mmHg at the arteriolar ends and 12-15 mmHg at the venous ends**. It can be measured at the fingernail beds directly (by a pipette inserted into a capillary and connected to a manometer) or indirectly (by finding the pressure necessary to occlude the capillaries). It is affected by the following factors :

(A) Pre-capillary factors

(1) Precapillary resistance : This is determined by the degree of contraction of the arterioles and precapillary sphincters. If it increases (by V.C.), the CP decreases and vice versa.

(2) Arterial blood pressure : If this increases, the CP would increase. However, in chronic hypertension the precapillary resistance is increased (due to arteriolar V.C.) and the CP is usually not significantly increased.

(B) Postcapillary factors

(1) Postcapillary resistance : The CP varies directly with this resistance. (thus, if it increases e.g. due to partial venous thrombosis, the CP increases).

(2) Venous pressure : The CP varies directly with changes in the venous pressure. Thus, if the venous pressure increases, the CP also increases (e.g. in cases of congestive heart failure and after prolonged standing).

CAPILLARY FRAGILITY (CF)

The capillaries are normally not fragile (i.e. they do not rupture easily) although they are very delicate. This is because according to *Laplace law* (page 93), the tension in the capillary walls is very low due to their extremely small radii. The CF is increased in many diseases e.g. scurvy (vitamin C deficiency) and purpura, and it can be checked by the following test:

Testing the capillary fragility (Hiss test)

The sphygmomanometer cuff is wrapped around the arm and inflated to a pressure of 80 mmHg for 8 minutes. This prevents the venous return from the forearm, resulting in rise of both the venous and capillary pressures, which leads to rupture of some capillaries forming tiny hemorrhages called *petechiae*. The latter are counted at the cubital fossa in a circular area 5 cm in diameter, and the CF is considered high if their number exceeds 3.

TRANSCAPILLARY EXCHANGE MECHANISMS

(1) DIFFUSION : This is the process by which substances move down a concentration gradient (from areas of high to areas of low concentration). Water and water-soluble substances (e.g. glucose, Na^+ , Cl^- and K^+) diffuse only through the capillary pores while fat-soluble substances diffuse across the whole capillary wall [so the diffusion of fat-soluble substances and O_2 and CO_2 is normally greater and faster than water-soluble substances].

(2) FILTRATION : This is the process by which fluid and the dissolved solutes are forced through the capillary membrane due to a difference in hydrostatic pressure on the 2 sides, and the amount of fluid filtered per unit time is proportionate to the difference in pressure as well as the capillary surface area and capillary permeability (see below).

(3) TRANSCYTOSIS (CYTOPEMPSIS OR VESICULAR TRANSPORT) This is the mechanism of transport of large molecules across the capillary membrane. These molecules are transported through the capillaries by **endocytosis** into their lining endothelial cells followed by **exocytosis** at the interstitial side of these cells. Normally, small amounts of protein leave the bloodstream to the interstitial fluid by this mechanism.

(4) DIAPYCNOSIS : This is the mechanism of transport of a whole cell across the capillary membrane e.g. leukocytes which leave the bloodstream toward areas of inflammation by this mechanism (refer to blood).

FORMATION AND DRAINAGE OF THE INTERSTITIAL FLUID (BULK FLOW ACROSS THE CAPILLARY MEMBRANE)

The interstitial fluid (IF) is continuously formed and drained at the capillaries, and it contains almost the *same constituents of the plasma except the plasma proteins* (which are minimally filtered because of their large sizes).

MECHANISM OF IF (= TISSUE FLUID) FORMATION AND DRAINAGE

2 main factors affect the IF (= tissue fluid) formation and drainage. These are the **Starling forces** (= the hydrostatic and osmotic forces that act across the capillary walls) and the **capillary permeability**.

THE STARLING FORCES

(1) **The hydrostatic capillary pressure (hcp)** : This promotes fluid movement outwards from the capillaries, and it is normally 32-35 mmHg at the arteriolar ends of capillaries and 12-15 mmHg at their venular ends.

(2) **The interstitial fluid pressure (ifp)** : This promotes fluid movement into the capillaries, and it normally averages 1 mmHg (see below).

(3) **The plasma osmotic (or oncotic) pressure (pop)** : This is produced mainly by plasma *albumin*. It averages 25 mmHg, and it promotes fluid movement into the capillaries.

(4) **The IF osmotic pressure (ifop)**: This promotes fluid movement outwards from the capillaries, and it normally averages 3 mmHg.

The (hcp) and (ifop) favour fluid filtration from the capillaries while the (pop) and (ifp) favour fluid reabsorption into the capillaries.

Considering the balance of the Starling forces at both ends of the capillaries, it is clear that *at their arteriolar ends, the filtering forces exceed the reabsorbing forces by 12 mmHg [(35 + 3) - (25 + 1)]* resulting in fluid filtration. *On the other hand, at the capillary venular ends, the reabsorbing forces exceed the filtering forces by about 8 mmHg [(25 + 1) - (15 + 3)]* resulting in fluid reabsorption.

Normally, about 24 litres of fluid are filtered daily through the capillaries. However, since the net reabsorbing force at the capillary venular ends is less than the net filtering force at their arteriolar ends, only about 85 % of the filtered fluid is reabsorbed into the capillary venular ends, and the remainder returns to the circulation *via the lymph vessels* (see below).

****** The Starling forces vary greatly in different organs depending on their functions. Also, there is evidence **that the interstitial fluid pressure (ifp) is negative in certain areas e.g. subcutaneous tissues (-2 to -3 mmHg)**

FACTORS THAT AFFECT THE CAPILLARY PERMEABILITY (CP)

The CP varies in different organs depending on their functions, and the *amount of the formed interstitial fluid is directly proportional to the CP*. Together with the available area for filtration, the CP determines the **filtration coefficient** i.e. the volume of fluid filtered / 1 mmHg / minute (normally 12.5 ml in the kidneys). The factors that affect the CP include the following :

(1) **Plasma Ca^{2+} concentration** : If the Plasma Ca^{2+} concentration increases, the CP is decreased (by narrowing the capillary pores), and vice versa.

(2) **Blood pH** : In acidosis, the Ca^{2+} in the capillary walls is dissolved, so the CP increases. Alkalosis produces an opposite effect.

(3) **Plasma proteins** : These partially close the capillary pores, so in case of hypoproteinemia, the CP is increased.

(4) **Vitamin C and glucocorticoid hormones** : These are essential for vitality and proper development of the capillary membrane, so in scurvy (vitamin C deficiency) and hypofunction of the adrenal cortex, the CP is increased.

(5) **Capillary diameter** : Capillary dilatation (by relaxation of the precapillary sphincters) widens the pores in their membranes, thus increasing the CP. This occurs by O_2 lack, some irritant gases (e.g. chlorine), excess heat or cold (the latter due to accumulation of V.D. metabolites as a result of ischemia) and by release of histamine (in inflammatory and allergic conditions).

The white reaction (white line)

Striking the skin lightly with a pointed object leads to pallor of the stimulated part within 15 seconds. This is due to direct contraction of the precapillary sphincters by the mechanical stimulus (which is followed by drainage of the blood out of the capillaries and small veins leading to pallor).

MECHANISMS OF V.D. IN THE SKIN

(1) Inhibition of the V.C.C. e.g. in cases of exposure to heat

(2) Release of V.D. substances, including (a) *Metabolites* (e.g. in reactive hyperemia, page 112) (b) *Substance P* (e.g. in the triple response (see next)

(c) *Bradykinin* which is released during sweat secretion (page 113) (d) *Histamine* that is released from damaged cells in cases of skin injury.



Figure 62 : The triple response.

The triple response

This is a response that results by firmly striking the skin with a pointed object. It consists of 3 reactions (figure 62) :

(1) Red reaction (or red line) : This appears in about 10 seconds at the site of the stroke. It is due to *capillary dilatation that occurs as a direct response of the capillaries to the stimulus.*

(2) Flare : This is diffuse mottled reddening that appears after the red reaction around the area of injury then gradually spreads outwards. It is due to *arteriolar V.D. that is produced by the antidromic local axon reflex mechanism through liberation of substance P* (page 113), *so it does not appear in locally anesthetized or denervated skin areas.*

(3) Wheal (swelling) : This is *local edema* that appears within a few minutes around the injured area. It is due to extravasation of fluid from the capillaries and postcapillary venules as a result of an increase of their permeability (which is produced by histamine that is released from the local mast cells and substance P that is released from the antidromic nerve terminals).

THE LYMPH CIRCULATION

This is concerned with return of the tissue fluid that is not reabsorbed at the capillaries (which is called **lymph**) back to the bloodstream. Lymph. is similar to the plasma except that it contains less proteins with a higher A/G ratio (since albumin is more easily filtered) and is rich in lymphocytes.

Lymph circulates in *non-innervated* vessels that form the lymphatic system. This system originates as minute blind lymphatic capillaries in the tissues, which unite forming larger lymphatic vessels, and these drain in the thoracic and right lymph ducts that open in the subclavian veins at the base of the neck. The **lymph nodes** are located along the course of the lymphatic vessels, and these vessels *have smooth muscle in their walls and contain valves* that allow unidirectional flow toward their central end.

FACTORS THAT MAINTAIN LYMPH FLOW

- (1) Rhythmic contraction of the smooth muscle in the walls of the lymphatic vessels.
- (2) Skeletal muscle contractions, which press on the lymphatic vessels (= muscle pump).
- (3) The negative intrathoracic pressure (= thoracic pump).
- (4) Gravity (which helps lymph flow from the upper parts of the body only).
- (5) The hydrostatic pressure of the interstitial fluid (in areas where it is +ve).
- (6) Arterial pulsations (by pressing on the near lymphatic vessels).

FACTORS THAT INCREASE LYMPH FLOW

The lymph flow increases whenever the tissue fluid increases due to :

- (1) V.D. of the arterioles or relaxation of the precapillary sphincters.
- (2) An increase of the venous pressure.
- (3) Tissue activity (the metabolites produce V.D. and increase the tissue fluid osmotic pressure, which causes more fluid filtration and increases the flow of lymph).
- (4) An increase of the blood volume e.g. by injection of isotonic saline.
- (5) **Lymphagogues** : These are substances that **increase the lymph flow**. They include a variety of agents that **increase capillary permeability** (e.g. histamine and bradykinin)..These substances were called **first class lymphagogues** in contrast to **hypertonic solutions** of glucose or NaCl, which were called **second class lymphagogues**. These solutions diffuse rapidly into the tissue spaces when i.v. injected, so the osmotic pressure of the interstitial fluid increases resulting in more fluid filtration and increased lymph flow.

Agents that cause contraction of smooth muscle also increase lymph flow from the intestines.

FUNCTIONS OF THE LYMPHATIC SYSTEM

- (1) Return of the tissue fluid that is not reabsorbed in the blood capillaries as and the filtered protein back into the bloodstream (*the lymph capillaries are much more permeable than the blood capillaries*).
- (2) Removal of bacteria from the tissues by the lymph nodes, which is an important defense function.
- (3) Drainage of lymphocytes from the lymph nodes into the bloodstream.
- (4) Absorption of the long chain fatty acids from the small intestine, which makes the lymph in the thoracic duct to have a *milky appearance*.

EDEMA

This is the presence of excess fluid in the bodt tissues. It is **2 types** :

(A) Intracellular edema

This is is produced as a result of either :

- (1) **Depression of cell membrane metabolic activity** (e.g.due to ischemia). In this case, the Na^+ pump is depressed (due to O_2 lack) so that excess Na^+ is retained inside the cells associated with water retention by osmosis
- (2) **Inflammation** : This increases the cell membrane permeability, which allows Na^+ and other ions to diffuse into the cells associated with water retention by osmosis

(B) Extracellular edema

This is accumulation of *excessive amounts of interstitial fluid* (mostly in the dependent parts of the body by the effect of gravity). It has 2 main causes :

(1) Excessive leakage of fluid from the capillaries due to either :

(a) An increase of the capillary hydrostatic pressure : This commonly occurs as a result of elevation of the venous pressure e.g. due to heart failure (producing *cardiac edema*) or *incompetent venous valves*

(b) Hypoproteinemia : This decreases the plasma osmotic pressure which reduces reabsorption of the tissue fluid. It may occur as a result of a decrease of synthesis of the plasma proteins (e.g. in *severe liver disease and undernutrition*) or excessive loss of plasma proteins (e.g. in the urine in case of the nephrotic syndrome, producing *renal edema*).

(c) An increase of capillary permeability : This increases filtration of both the tissue fluid and the plasma proteins. The latter further increases filtration by increasing the osmotic pressure of the interstitial fluid. It occurs due to either inflammation, allergic reactions (due to release of histamine), vitamin deficiency (specially vitamin C) and excessive heat.

(d) Salt & water retention (specially in renal diseases) : This increases the blood volume, capillary pressure and fluid filtration into the tissue spaces

(2) Inadequate lymph drainage

Blockage of the lymph vessels leads to accumulation of fluid and protein in the tissue spaces. The latter also increases fluid filtration by increasing the osmotic pressure of the tissue fluid. This condition is called **lymphedema**, and in chronic conditions it leads to fibrosis of the interstitial tissue, and the edema becomes non-pitting. It commonly occurs after certain surgical operations (e.g. radical mastectomy) and by infection with the *filaria worms*. These worms obstruct the lymphatics, causing massive swelling of the affected organ (commonly the legs or scrotum), a condition called **elephantiasis**.

SAFETY FACTORS AGAINST PRODUCTION OF EDEMA

(1) The -ve interstitial fluid hydrostatic pressure (e.g. in subcutaneous tissues, page 119). The -ve pressure holds the tissues together *thus decreasing its compliance (distensibility)*. Accordingly, small increases in the tissue fluid markedly increase the hydrostatic pressure of the interstitial fluid, which opposes further fluid filtration and also increases the lymph flow.

(2) Increasing the lymph flow : The lymph flow increases 10-50 fold when fluid begins to accumulate in the tissue spaces. This removes large amounts of the interstitial fluid and limits development of edema.

(3) Washdown of interstitial fluid protein : The increased lymph flow decreases the protein content and osmotic pressure of the interstitial fluid, which reduces filtration in the capillaries and limits development of edema.

CHAPTER 12

THE VENOUS CIRCULATION

Veins are thin-walled non-pulsatile vessels that contain more than 50 % of the circulating blood volume under a low pressure. Their main functions are (1) *Returning blood from the tissues to the right atrium* (see factors that affect the venous return, page 82) (2) *Storage of variable amounts of blood* (acting as a blood reservoir because they are *capacitance vessels*).

THE NORMAL VENOUS PRESSURE

(A) In the recumbent position (absent effect of gravity) : About 15 mmHg in the venules, 7 mmHg in the cubital veins, 12 mmHg in the ankle veins, 11 mmHg in the upper abdominal veins, 6 mmHg in the veins just below the diaphragm, 4.6 mmHg in the thoracic veins at their entrance into the right atrium (= *central venous pressure*) and 2 mmHg in the right atrium

(B) In the standing position (under effect of gravity) : About 35 mmHg in the dependent veins of the hands, 80-90 mmHg in the ankle veins, 11 mmHg in the upper abdominal veins, 4 mmHg in the veins just below the diaphragm, 2 mmHg in the thoracic veins (*central venous pressure or CVP*), zero mmHg in the right atrium and head veins (*but subatmospheric in the dural sinuses e.g. it is -10 mmHg in the superior sagittal sinus*).

MEASUREMENT OF THE VENOUS PRESSURE

(A) DIRECT METHODS : The peripheral venous pressure is measured through a needle inserted into the vein and connected to a saline manometer. The CVP is measured through a cardiac catheter introduced into the thoracic veins (via the cubital vein) and connected to the measuring device.

(B) INDIRECT METHODS : The peripheral venous pressure can be measured by the *hand to heart method*. The examiner slowly elevates the patient's hand and observes the level at which its dorsal veins collapse (figure 63). The venous pressure roughly equals the distance between that level and the sternal angle in cm blood (1 cm blood = 0.77 mmHg).

The CVP can be measured while the patient is in *the semisitting position with his head raised 45 °* (figure 63). The upper level of the congested part of the external jugular vein is noticed, and the CVP roughly equals the distance between that level and the sternal angle (in cm blood). Normally, about the lower third of this vein is congested (level of the right atrium) and it becomes more congested if the CVP is increased e.g. in heart failure.

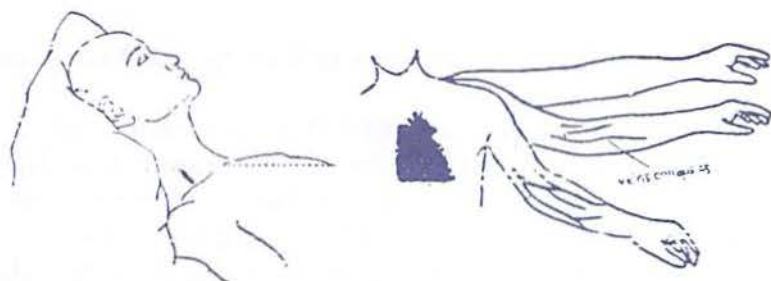


Figure 63 : Indirect measurement of the CVP (left), and peripheral venous pressure by the hand to heart method (right).

FACTORS THAT AFFECT THE VENOUS PRESSURE

- (1) **Gravity :** On standing, the CVP drops while the peripheral venous pressure (PVP) increases e.g. in the ankle (see below).
- (2) **Blood volume :** Both the CVP and PVP are increased in hypervolemia and decreased in hypovolemia.
- (3) **Arteriolar diameter :** Arteriolar V.D. increases both the PVP and CVP, while arteriolar V.C. decreases them.
- (4) **Capillary diameter :** Widening of the capillary diameter (by relaxation of the precapillary sphincters) leads to pooling of blood in the capillaries, resulting in reduction of both the PVP and CVP.
- (5) **Venomotor tone :** Its increase (i.e. *venoconstriction*) e.g. by sympathetic stimulation increases both the PVP and CVP, and vice versa.
- (6) **Blood outflow from the veins :** Its decrease leads to an increase of both the CVP and PVP, and vice versa. A decrease of blood flow from the veins occurs in congestive heart failure and when the intrapericardial or intrathoracic pressure increases.
- (7) **Acceleration forces :** Upward vertical acceleration causes blood to move downwards, so the venous pressure is decreased in the head while it is increased in the lower limbs. On the other hand, downward vertical acceleration produces opposite effects (see next).

EFFECTS OF ACCELERATION ON THE CVS

The force of acceleration is expressed in g (= gravity) units. It produces no effects if it acts across the body in the chest to back direction (so astronauts in the space crafts lie in the recumbent position). On the other hand, gravitational forces acting along the vertical axis of the body *cause the blood to move in an opposite direction to that of acceleration* leading to the following effects ::

(a) **Alteration of the venous pressure in the upper and lower parts of the body** (see above).

(b) **Blackout and redout reactions** : If the direction of the acceleration force was upwards, a positive g force acts from head to foot. This shifts the blood from the upper parts of the body to be pooled in the lower limbs, resulting in temporary block of retinal function and loss of vision (=blackout) followed by fainting due to cerebral ischemia (blackout precedes fainting because the intraocular pressure is higher than the intracranial pressure).

On the other hand, if the direction of the acceleration force was downward, a negative g force acts from foot to head. This shifts the blood from the lower parts of the body to be pooled in the upper parts, resulting in severe pain in the head and congestion of the retinal vessels, which causes the visual fields to appear red (= **redout**) and may also lead to temporary blindness.

EFFECTS OF GRAVITY ON THE CVS

On changing from the recumbent to the upright posture, gravity leads to pooling of 300-500 ml of blood in the lower limbs. **With prolonged quiet standing**, this leads to the following effects :

- (1) An increase of the arterial pressure below the heart level (becoming 180-200 mmHg in the feet) and its decrease above the heart level due to reduction of the VR, SV and CO (becoming 60-75 mmHg at the head level, which may lead to **fainting as a result of cerebral ischemia**)
- (2) An increase of the venous pressure below the heart level (becoming 85-90 mmHg in the feet) and its decrease above the heart level (becoming zero mmHg at the head level).
- (3) An increase of the capillary pressure in the lower limbs (due to the increased venous pressure) which leads to excess fluid filtration (**ankle edema**).
- (4) If the venous valves are abnormal or incompetent, prolonged standing may also lead to occurrence of **varicose veins**.

Body adjustments against the effects of gravity

As long as the individual moves about after standing, the effects of gravity are greatly decreased by the following mechanisms :

- (1) A normal VR is almost maintained constant by the effects of *the thoracic and muscular pumps, the venomotor tone and the cardiac suction forces* (page 83), so that the venous pressure at the feet remains below 30 mmHg..
- (2) **Initiation of arterial baroreflexes** : The initial drop of the arterial blood pressure in the arterial baroreceptors results in stimulation of the VCC, which increases the arterial blood pressure by the following effects :

- (a) Heart acceleration (which helps maintenance of the cardiac output)
- (b) Arteriolar V.C. (which increases the peripheral resistance)
- (c) Venoconstriction (which prevents pooling of blood in the lower limbs and helps increasing the venous return)
- (d) Secretion of catecholamines from the adrenal medullae (which augments all previous effects).

(3) Release of renin from the kidneys : This occurs as a result of renal ischemia caused by the initial drop of the cardiac output and arterial blood pressure. It leads to formation of angiotensin II, which causes *potent V.C.* and *stimulates aldosterone secretion* from the adrenal cortex, in addition to other effects (page 108). Aldosterone promotes Na^+ and water retention in the body, which increases both the blood volume and arterial blood pressure.

(4) Cerebral autoregulation : As a result of the decreased cerebral blood flow, the PCO_2 increases while the PO_2 and pH decrease. These effects cause local V.D., so the cerebral blood flow is reduced only by 20 %. In addition, the O_2 extraction ratio increases, so the cerebral O_2 consumption is not markedly decreased.

Orthostatic (postural) hypotension

This is fall of the arterial blood pressure that occurs on sudden standing, *due to inefficient antigravity compensatory mechanisms* (see above). It is accompanied by dimness of vision, dizziness and even fainting (= *orthostatic syncope*). It is *uncommon in normal persons*, but it commonly occurs as a result of **depression of the sympathetic functions**, which is encountered in the following conditions :

- (a) Patients receiving sympatholytic drugs.
- (b) Diseases that damage the sympathetic nervous system e.g. diabetes and syphilis.
- (c) **Primary autonomic failure** (= a condition characterized by a decrease of production of catecholamines due to congenital deficiency of the dopamine beta-hydroxylase enzyme).

CHAPTER 13

THE CORONARY CIRCULATION

The coronary vascular system (vasculature)

- (1) 2 coronary arteries supply the heart. They arise from the aorta just above the aortic valve (figure 64).
- (2) In 50 % of people, the right artery is dominant i.e. has a greater blood flow than the left artery (in 20 % of people, there is left dominance and in 30 % , the flow is equal in both arteries).
- (3) The large coronary arteries are present in the epicardium, and they give smaller branches that dip inwards towards the endocardium.
- (4) The capillary density is high in the myocardium (300 capillaries / mm²).
- (5) The coronary venous blood is returned mostly to the right atrium by the *coronary sinus and anterior cardiac veins*, and a small amount is drained *directly into all cardiac chambers* by small vessels called **thebesian veins**.
- (6) Few collaterals exist between the coronary arterioles. They are insufficient to compensate for acute obstructions in the large arteries (so the coronary arteries are considered *end arteries*). However, efficient collaterals can develop if the arterial obstruction was occurring gradually..

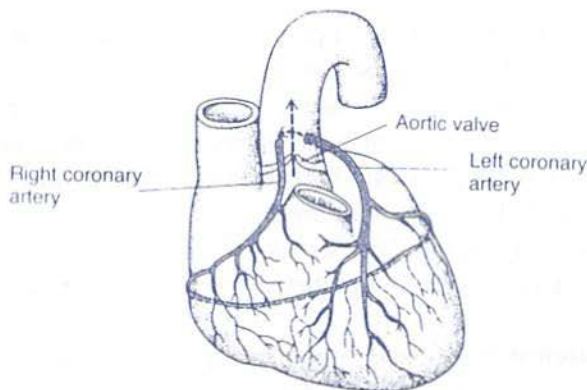


Figure 64 : The coronary arteries.

THE CORONARY BLOOD FLOW (CBF)

The total CBF (normally about **250 ml /minute**) can be determined by **Kety method** which depends on applying the **Fick principle** (page 79): The subject breathes nitrous oxide (N₂O), and an arterial blood sample (obtained from any artery) and a venous blood sample from the heart (obtained from the coronary sinus by a cardiac catheter) are analysed for N₂O concentration. By applying the Fick principle, *the CBF = amount of N₂O taken by the heart per minute / Arterial N₂O concentration – Venous N₂O concentration*.

****** Estimation of the *coronary blood flow in different regions* of the heart is useful for detection of ischemic areas. It can be done by i.v. injection of radioactive tracers (e.g. **thallium-201**) and for the first 10-15 minutes after injection, its distribution in the heart is detected with radiation detectors placed on the chest. Its distribution is directly proportionate to the myocardial blood flow and areas of ischemia can be detected by their low intake.

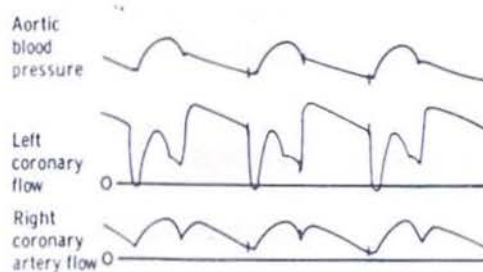


Figure 65 : The CBF in both coronary arteries during the cardiac cycle.

FACTORS THAT AFFECT (CONTROL) THE CBF

(A) METABOLIC FACTORS

The CBF is directly proportionate to the myocardial O_2 requirement. Accordingly, the CBF increases during cardiac activity and such increase occurs as a result of V.D. of the coronary vessels by the produced metabolites. The major coronary V.D. metabolite is **adenosine** (which is formed as a result of ATP breakdown in response to O_2 lack). However, CO_2 , K^+ , H^+ , prostaglandins and NO (page 112) may also contribute in V.D. of the coronary vessels.

Coronary autoregulation

Within a mean aortic pressure range between 60-140 mmHg, the CBF is kept constant. *Such autoregulation of the CBF depends on metabolic factors* (e.g. a fall of the aortic pressure decreases the CBF. This leads to O_2 lack and accumulation of metabolites, and both cause V.D., so the CBF increases and is kept almost constant). The phenomenon of **reactive hyperemia** (page 112) also occurs in the cardiac muscle by effect of the V.D. metabolites.

(B) MECHANICAL FACTORS

(1) The CBF undergoes phasic changes **during the cardiac cycle**. During systole, the coronary vessels are compressed by the contracting myocardium leading to reduction of the CBF. This occurs *especially in the left coronary artery* due to the thick left ventricular wall. For this reason,

most of the blood flow in left coronary artery occurs during diastole, being maximal at the end of the isometric relaxation phase (figure 75). Such changes are not apparent in the right coronary artery (because the force of contraction in the thin right ventricle is weaker than in the left ventricle) and the blood flow in right coronary artery occurs during both systole and diastole, and is even greater during systole (figure 75).

(2) The CBF is affected by changes in the heart rate. In cases of tachycardia, there is shortening of the diastolic periods (during which the coronary flow is maximal), so the CBF is decreased. An opposite effect occurs in cases of bradycardia.

(C) NEURAL (NERVOUS) FACTORS

Stimulation of the cardiac sympathetic nerves causes *coronary V.C. by a direct action on the alpha receptors* (which tends to decrease the CBF). However, the simultaneous increase of the cardiac activity results in excessive formation of metabolites that counteract the direct V.C. effect and lead to coronary V.D., resulting in a net increase of the CBF. Vagal stimulation dilates the coronary vessels, but its role in the control of CBF is unsettled.

Regional distribution of myocardial blood flow

The intramyocardial pressure in the left ventricular wall during contraction is much greater in the inner (subendocardial) layer than in the outer (subepicardial) layer. Thus, **during systole** the blood vessels in the inner layer are normally severely compressed and *the CBF in the subendocardial layer of the left ventricle may stop completely*. However, this is compensated by V.D. during diastole, so that a normal CBF in this layer is maintained.

Why ischemia and infarction are common in the subendocardial layer of the left ventricle ? What is coronary steal ?

This is because the subendocardial layer of the left ventricle receives its blood supply **during diastole only** (while all other parts of the left and right ventricular walls receive blood supply during both systole and diastole), which renders this layer more liable to ischemia and infarction in cases of coronary obstruction. This specially occurs if the cardiac activity is increased because V.D. produced in the outer normal myocardial layers (by effect of the metabolites formed as a result of cardiac activity) leads to shift of blood to these layers from the already ischemic inner layers, which further decreases the blood supply to the subendothelial layer. This shift of blood has been called. **coronary steal**.

THE CORONARY FLOW RESERVE

Energy production in the heart requires a high rate of O_2 consumption because it is almost completely dependent on aerobic (oxidative) mechanisms.

The normal CBF at rest is about 250 ml / minute (5 % of the cardiac output), and it delivers to the heart about 29 ml O_2 / minute (page 91). Normally, the cardiac muscle extracts 70 - 80 % of the arterial O_2 content as blood flows through the heart muscle, and as a result of such *high O_2 extraction ratio*, the venous O_2 reserve (i.e. the amount of O_2 present in the coronary venous blood) is normally small. Accordingly, *the venous O_2 reserve plays a minor role in supplying extra O_2 to the heart during activity*, and **additional O_2 can be supplied only by increasing the CBF**. During maximal cardiac activity, the CBF can increase up to 1000 ml / minute or more as a result of coronary V.D. (which increases the myocardial O_2 consumption 4-5 fold), a mechanism that is called **coronary flow reserve**.

Functional characteristics of the coronary circulation

- (1) It is a vital circulation that is closely related to cardiac function.
- (2) It is a short rapid circulation.
- (3) The high O_2 extraction by the cardiac muscle results in a small venous O_2 reserve (*so O_2 consumption during cardiac activity can be increased significantly only by increasing the CBF*).
- (4) It is the only circulation in which blood flow in certain heart areas occurs only during diastole (the left ventricular subendocardial muscle layer).
- (5) There is poor and inefficient anastomoses between the coronary vessels.
- (6) It is a rich circulation (about 5 % of the cardiac output although the heart weighs only about 300 gm i.e. 0.05 % of the body weight).
- (7) Its regulation is mainly by metabolic (and not neural) factors.

CORONARY HEART DISEASE (CORONARY INSUFFICIENCY)

This is produced as a result of narrowing of the coronary arteries commonly due to **atherosclerosis** and it causes angina pectoris or myocardial infarction

Angina pectoris

This is severe attacks of precordial pain that occur when cardiac activity increases (e.g. in cases of effort and excitement). It is mostly substernal and it often radiates to the left shoulder and left arm. It is a type of **ischemic pain** that is initiated as a result of stimulation of certain pain nerve endings in the myocardium by a metabolite called **Lewis P factor** (which might be K^+ , H^+ , histamine, proteolytic enzymes or otherwise). This pain is absent at rest, and can also be relieved by rest (due to wash of the causing metabolite).

Angina may occur in absence of coronary occlusion specially in cases of aortic stenosis, because a stronger left ventricular contraction should occur to expel blood through the narrow aortic valve (which severely compresses the coronary vessels and also increases the myocardial O_2 requirement)

The anginal pain can be relieved by the following drugs :

(1) **Nitrates (e.g. nitroglycerin)** : These substances are the best coronary V.D. drugs. They also dilate the systemic arterioles and venules, and this is beneficial since arteriolar V.D. decreases the cardiac afterload while venodilatation decreases the venous return and the stroke volume, and both effects decrease the myocardial activity and O_2 consumption

(2) **Beta-adrenergic blocker drugs** (e.g. atenolol) : These reduce the myocardial O_2 consumption by decreasing the heart rate and power of contraction.

(3) **Ca^{2+} channel blockers** : These act like the beta-adrenergic blockers and in addition, they produce coronary V.D.

Myocardial infarction

This is necrosis (death) of a myocardial area as a result of severe (or prolonged) ischemia e.g. due to sudden occlusion of a coronary branch by a thrombus.. Irreversible changes occur in the affected muscle fibres ending by fibrosis. Immediate death may occur due to either acute heart failure and pulmonary edema or ventricular fibrillation. However, in long-standing cases, the affected area gradually bulges out during systoles (= *systolic stretch*) and it may rupture suddenly leading to death.

The dead cardiac muscle fibres leak certain enzymes and other substances into the bloodstream and measuring the rises of their blood levels greatly helps in the diagnosis and prognosis of infarction. The commonly measured substances are **the isomer of creatine kinase as well as troponins T and I**.

The effects of myocardial infarction can be decreased *if within the first few hours after the attack*, an agent that accelerates lysis of the intracoronary thrombus is i.v. administered e.g. TPA (tissue plasminogen activator).

In patients suffering angina, the occurrence of infarction can be prevented by certain surgical procedures e.g. (1) **Angioplasty** i.e. stretching of the narrowed coronary area by a balloon catheter (2) **Coronary bypass** i.e. connecting the aorta to the coronary artery beyond the area of narrowing by a graft taken from any vein (commonly the saphenous vein).

Cardiac transplants are indicated if the left ventricular ejection fraction is less than 15 % or if there is severe uncontrollable ventricular arrhythmia. A transplanted heart can achieve 70 % of the maximal cardiac output produced by normal hearts, although it is denervated and is controlled only chemically and by the Starling mechanism

CHAPTER 14

THE CEREBRAL CIRCULATION

The cerebral vascular system (vasculature)

- (1) The brain receives arterial blood supply from the 2 internal carotid and the 2 vertebral arteries (the latter unite to form the *basilar artery*). These arteries constitute the **circle of Willis** at the base of the brain (figure 66).
- (2) There is no crossing in this circuit i.e. substances injected into one carotid artery are distributed almost only to the cerebral hemisphere on that side.
- (3) There are few anastomoses between the cerebral arterioles that are insufficient to prevent cerebral infarction if a large artery is obstructed, so the cerebral arteries are considered *end arteries*.
- (4) The cerebral capillaries generally have a low permeability because (a) They are non-fenestrated (b) There are tight junctions between their endothelial cells (c) The glial cells (= astrocytes) have end feet that cover large areas of the capillary walls (d) Transecytosis (vesicular transport) is minimal.
- (5) Venous drainage from the brain occurs by way of the deep veins and dural sinuses, which empty mainly into the *internal jugular veins*. A small amount of venous blood drains through the *emissary veins to the scalp*.

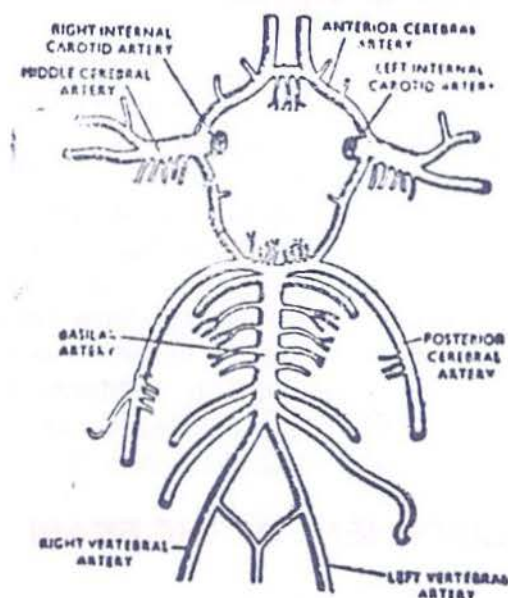


Figure 66 : The circle of Willis (circulus arteriosus).

THE BLOOD BRAIN BARRIER (BBB)

The low permeability of the cerebral capillaries limits the passage of many substances and drugs from the blood to the brain, a phenomenon called the blood brain barrier (BBB). However, water, O_2 , CO_2 and lipid-soluble substances (as alcohol and anesthetic drugs) cross such barrier easily. On the other hand, passive glucose transport across the BBB is slow, but it is facilitated by 2 forms of glucose transporter I (GLUT I).

The BBB helps maintenance of the ionic composition and pH of the neural environment constant. It also protects the brain from exogenous and endogenous toxins and prevents escape of the neurotransmitters into the blood. It is *weak in infants*, so infants having jaundice may suffer severe neurological symptoms (because bilirubin in this case crosses the BBB and causes damage specially to the basal ganglia, a condition called **kernicterus**).

The BBB breaks down in areas of infection, injury and tumours. Such effect helps to identify the location of tumours. When radioactive-iodine labeled albumin (which does not penetrate normal brain tissue) is i.v. injected, it enters the tumour tissue resulting in its radioactivity (the detection of which greatly helps in localization of the site of the tumour).

The circumventricular organs

These are 4 structures located above the brain stem in relation to the hypothalamus that have fenestrated highly-permeable capillaries (so they are said to be **outside the BBB**). They are 2 types :

(A) **Neurohemal organs** (= structures that secrete hormones which readily enter the circulation). They include the *neurohypophysis* (which secretes the ADH and oxytocin) and the *hypothalamic median eminence* which secretes the hypophysiotropic hormones (refer to endocrines).

(B) **Chemoreceptor organs** (= structures at which circulating substances act to initiate certain effects). They include the **area postrema** (the *chemoreceptor zone* that initiates vomiting), the **subfornical organ** and the **organum vasculosum of the lamina terminalis**. Angiotensin II induces water intake and other effects by acting on the latter 2 organs (page 108).

OXYGEN REQUIREMENT OF THE BRAIN

The O_2 consumption of an adult brain at rest is about 50 ml / minute (i.e. about 1/5 of the total O_2 consumption). The brain is **very sensitive to hypoxia** (specially the cerebral cortex and basal ganglia), so occlusion of the blood supply to the brain produces unconsciousness in about 10 seconds.

BRAIN METABOLISM

The major source of energy of the brain is **glucose**, so the R.Q. of the cerebral tissue is 0.95-0.99 (refer to metabolism), and *insulin is not required by most cerebral cells for its utilization*. During prolonged starvation, however, other substances can be metabolized (e.g. amino acids). *Although both oxygen and glucose are needed for brain metabolic activity, it can withstand hypoglycemia for longer periods than it can withstand hypoxia* (see above).

The brain cells also take up *glutamate from the blood, where it combines with ammonia forming glutamine*. This is an important detoxifying mechanism since *ammonia is very toxic to the nerve cells*.

THE CEREBRAL BLOOD FLOW (CBF) & ITS CONTROL

The adult human brain weighs about 1400 gm and the total average CBF is about 750 ml / minute. It can be measured by the **Kety method**, which depends on application of the **Fick principle** after inhalation of nitrous oxide (N_2O), similar to measurement of the coronary blood flow (page 128).

The total CBF is generally maintained constant under varying conditions. However, it is not uniform in all parts of the brain e.g. it is *much greater in the gray matter than in the white matter*. The regional CBF also shows marked fluctuations both in the normal condition (e.g. it increases in active areas) as well as in disease (e.g. it increases in epileptic foci and decreases in the parietal cortex and the neighbouring areas in Alzheimer's disease).

The CBF is controlled (regulated) by the following factors :

(A) PHYSICAL FACTORS

(1) **The arterial and venous pressures at the brain level** : The CBF is directly proportionate to the difference between these pressures (which is called the *effective perfusion pressure*).

(2) **Blood viscosity** : The CBF varies inversely with the blood viscosity.

(3) **Intracranial pressure** : The brain, CSF and cerebral vessels are enclosed in the rigid skull, and normally their total volume is kept relatively constant at any time (= **Monro-Kellie doctrine**). The brain tissue and CSF are incompressible while the cerebral vessels are compressed whenever the intracranial pressure rises (which decreases the CBF) and dilated whenever the intracranial pressure falls (which increases the CBF).

(B) CHEMICAL FACTORS

The cerebral arterioles are extremely sensitive to **hypoxia and hypercapnia**. These and other metabolites (e.g. K^+ and adenosine) produce a *potent V.D. effect in active areas*. Rise of PCO_2 exerts a particularly potent dilator effect by increasing the local H^+ concentration while a fall in PCO_2 (e.g. during hyperventilation) has a V.C. effect. On the other hand, a drop of PO_2 causes V.D. while a rise of PO_2 causes mild V.C.

AUTOREGULATION OF THE CBF

Autoregulation in the brain maintains the CBF almost constant at an arterial pressure range of **65-140 mmHg**. A fall in arterial pressure reduces the CBF, leading to accumulation of metabolites that produce V.D. (see above) so the CBF tends to increase to the normal level. On the other hand, rise of the arterial pressure increases the CBF leading to wash of the V.D. metabolites which results in V.C., so the CBF tends to decrease to the normal level..

(C) NERVOUS FACTORS

The cerebral vessels receive V.C. sympathetic and V.D. parasympathetic nerves from the superior cervical and sphenopalatine ganglia respectively. Although sympathetic stimulation causes V.C. yet the CBF is not reduced due to the simultaneously-increased arterial pressure. Such sympathetic V.C. effect is important when (a) The arterial pressure is much elevated e.g. in severe exercise (to prevent rupture of the cerebral vessels and disruption of the BBB) (b) A cerebral vessel is injured (to limit intracranial hemorrhage).

THE CEREBROSPINAL FLUID (CSF)

This fluid (normal volume about 150 ml) is formed by an active transport mechanism (mostly by the choroid plexuses in the lateral ventricles of the cerebral hemispheres).. It passes to the 3rd ventricle then through the aqueduct of Sylvius to the 4th ventricle and central canal of the spinal cord. It then flows outward to fill the subarachnoid space around the brain and spinal cord. It is absorbed mainly through the arachnoid villi by bulk flow into the cerebral venous sinuses at a rate that is proportionate to its pressure (which averages normally about **130 mm water or 10 mmHg**).

Composition of CSF

This is different from the plasma due to a **blood - CSF barrier** (the CSF pH is lower, and it has lower concentrations of K^+ , Ca^{2+} , protein, glucose, inorganic P, urea, cholesterol, uric and lactic acids). On the other hand, it has higher concentrations of Mg^{2+} , Cl^- and creatinine as well as a higher PCO_2 .

Functions of CSF

The main function of CSF is **protection of the brain from damage**. The brain actually floats in the CSF (so its net weight becomes only 50 gm), and the CSF forms a fluid cushion around the brain. This absorbs mechanical shocks applied to the head and prevents concussion, but strong blows may cause brain injury at a point opposite to that of the blow (*contrecoup injury*).

The CSF also helps (a) Maintenance of the intracranial pressure (b) Brain nutrition (c) Removal of waste products from the brain (d) Transport of various neuronal secretions.

CHAPTER 15

THE PULMONARY CIRCULATION

Functions of the pulmonary circulation

- (1) Conduction of blood from the right side of the heart to its left side.
- (2) Blood oxygenation and wash of CO_2 (= arterialization of venous blood).
- (3) Filtration of various emboli (e.g. thrombi) from the venous blood.
- (4) Blood reservoir of a varying capacity (specially the pulmonary veins).

The pulmonary vascular system (vasculature)

The lungs receive arterial blood from the *pulmonary and bronchial arteries* (the latter arise from the aorta), and their venous blood is drained mainly by the *4 pulmonary veins*. The pulmonary vasculature is characterized by :

- (1) The wall of the pulmonary artery is thin while the pulmonary arterioles are short, wide and contain little smooth muscle. These properties render the pulmonary arterial tree **highly-compliant** (i.e. easily distensible).
- (2) The pulmonary veins are short and compliant as the systemic veins.
- (3) Considerable anastomoses exist between the branches of the pulmonary and bronchial arteries.
- (4) The pulmonary capillaries are highly permeable and have a large surface area (about 70 m^2) as well as multiple anastomoses.

Normal pressures in the pulmonary circulation

- In the **right ventricle**, the systolic pressure is about 25 mmHg, while the diastolic pressure is about 0 mmHg.
- In the **pulmonary artery**, the systolic pressure is 25 mmHg (about 1/5 that in the aorta since the pulmonary vessels offer smaller peripheral resistance), while the diastolic pressure is 9 mmHg (mean pressure 15 mmHg).
- In the **pulmonary capillaries**, the pressure is 7-10 mmHg.
- In the **pulmonary veins and left atrium**, the pressure is about 5 mmHg.

THE PULMONARY VASCULAR RESISTANCE (PVR)

The PVR is normally about 1/6 that in the systemic circulation because of the *large distensibility of the pulmonary vasculature*. Factors that produce V.C. (e.g. symp.stimulation, angiotensin II and endothelin) increase the PVR, while those producing V.D. (e.g. vagal stimulation, histamine and bradykinin) decrease it (the latter 2 probably through releasing NO)..

The PVR also increases significantly in certain lung diseases e.g. emphysema, pulmonary fibrosis and pulmonary embolism, as a result of (a) Obliteration of the pulmonary vessels (b) Local hypoxia in the lungs (c) Reflex sympathetic stimulation (in case of pulmonary embolism).

REGULATION OF THE PULMONARY BLOOD FLOW (PBF)

The PBF *equals the cardiac output*, and it is regulated as follows :

- (1) **Overall regulation of the PBF** : This is a *passive process* e.g. during exercise, the cardiac output increases and the pulmonary vessels dilate passively (due to their high distensibility) so the PBF increases proportionately
- (2) **Regional regulation of the PBF** : This is controlled by 2 factors :
 - (a) **O₂ tension** : Local hypoxia causes V.C. by directly stimulating the vascular smooth muscle. Such effect shifts the blood away from the hypoxic area to other normally ventilated alveoli without affecting the total PBF. Local CO₂ accumulation decreases the pH in the area, which also causes V.C..
 - (b) **Gravity** : Under the effect of gravity in the upright position, the PBF in the apices of the lungs is decreased, then it increases gradually from above downwards becoming maximal in the lung bases (= **waterfall effect**).

FACTORS THAT AFFECT PULMONARY ARTERIAL B.P.

(A) Pulmonary vascular resistance (PVR)

Factors that increase the PVR increase the pulmonary arterial B.P. and vice versa. These factors include the following :

- (1) **Nervous factors** : Sympathetic stimulation causes V.C. of the pulmonary arterioles, which increases the PVR and pulmonary arterial B.P. Vagal stimulation produces opposite effects.
- (2) **Chemical factors** : Pulm. V.C. substances (e.g. angiotensin II, endothelin and thromboxane) increase the PVR and pulm. arterial B.P. while V.D. substances (e.g. histamine, bradykinin and ANP) produce opposite effects.
- (3) **Systemic hypoxia** : This leads to V.C. all over the pulmonary arterioles, which increases the PVR and pulmonary arterial B.P.
- (4) **Respiratory movements** : During inspiration, the pulmonary arterioles dilate resulting in reduction of both the PVR and pulmonary arterial B.P. During expiration, opposite effects occur.
- (5) **Lung diseases** : The diseases that cause narrowing of the pulmonary arterioles (e.g. emphysema, pulmonary fibrosis and pulmonary embolism) increase both the PVR and the pulmonary arterial B.P. .

(B) Left atrial pressure

A rise of the left atrial pressure (e.g. secondary to left ventricular failure or severe mitral stenosis) leads to back pressure in the pulmonary vascular system resulting in elevation of the pulmonary arterial B.P..

(C) Cardiac output

An increase in the cardiac output leads only to a small rise of the pulmonary arterial B.P. because of the large capacity of the pulmonary vascular bed.

PULMONARY HYPERTENSION

This condition is diagnosed when the pulmonary arterial blood pressure exceeds 30 / 15 mmHg. It may occur as a result of (1) Rise of the left atrial pressure e.g. due to left ventricular failure or severe mitral stenosis (2) Lung diseases that increase the PVR e.g. emphysema, diffuse pulmonary fibrosis and pulmonary embolism. These diseases may lead to right ventricular failure, a condition that is called **cor pulmonale** (i.e. congestive heart failure secondary to a pulmonary disease).

FLUID EXCHANGE IN THE PULMONARY CAPILLARIES

The formation and drainage of interstitial fluid in the lungs are controlled by the **Starling forces** as follows :

(1) Forces that favour fluid filtration :

a- The pulmonary capillary hydrostatic pressure (7-10 mmHg).

b- Interstitial fluid colloid osmotic pressure (about 14 mmHg).

c- Interstitial fluid pressure (-5 to -8 mmHg).

(2) Force that favour fluid absorption : This is the plasma colloid osmotic pressure (25 - 28 mmHg).

Normally, the filtration forces exceed the reabsorbing force resulting in slight fluid filtration in the pulmonary interstitium. However, the alveoli are kept dry i.e. free of fluids (for adequate gas exchange) by 2 mechanisms

(a) The negative pressure in the lung interstitial spaces sucks out excess fluid in the alveoli through openings between the alveolar epithelial cells.

(b) The rich lymphatic drainage of the lungs removes excess fluids that may accumulate around the alveoli.

PULMONARY EDEMA

This is accumulation of excess tissue fluid in the lungs. It starts in the interstitial spaces, then fluids may diffuse into the alveoli (leading to death in severe cases as a result of suffocation). Its main causes are :

(1) Rise of the pulmonary capillary hydrostatic pressure (commonly due to either left ventricular failure or severe mitral stenosis).

(2) Damage of the pulmonary capillary membranes (due to infections e.g. pneumonia, or inhalation of irritant gases e.g. chlorine).

(3) Obstruction of lymph drainage from the lungs e.g. by thoracic tumours.

****** Pulmonary edema also occurs in the *respiratory distress syndrome* (refer to respiration) and is *favoured by hypoproteinemia* (due to lowering of the plasma colloid osmotic pressure).

Safety factors that limit pulmonary edema

(1) The normal low pulmonary capillary pressure and high plasma colloid osmotic pressure : This provides a significant safety factor because pulmonary edema will not occur except when the pulmonary capillary pressure (7-10 mmHg) exceeds the plasma colloid osmotic pressure (25-28 mmHg).

(2) The normal negative interstitial fluid pressure (-5 to -8 mmHg) : This sucks out excess fluid from the alveoli.

(3) The rich supply of the lungs with lymph vessels : This drains excess interstitial fluid and decreases the filtering force (by reducing the interstitial fluid colloid osmotic pressure as a result of protein washdown).

Functional characteristics of the pulmonary circulation

(1) The pulmonary vascular system is a *distensible low pressure system*.

(2) It is a *high flow circulation* (the pulmonary blood flow = cardiac output)

(3) *Changes in the pulmonary vascular resistance are limited* due to the poor smooth muscle in the pulmonary arteriolar walls.

(4) Its *venous return at the left atrium is 1-2 % greater than the right ventricular output* (due to excess blood drained from the bronchial veins).

(5) It has a high compliance, acting as a *blood reservoir of varying capacity*.

(6) The *blood flow in the pulmonary capillaries is rapid* (about 0.75 second during rest and 0.3 second during exercise).

(7) It has an *extensive pulmonary capillary surface area* together with a *high capillary permeability*.

(8) The *pulmonary blood flow is affected by gravity* (it is much greater in the bases of the lung than in their apices).

(9) The alveoli are normally *kept dry*.

(10) It has *special reactions to gas changes* i.e. hypoxia, hypercapnia and excess H^+ produce V.C. (and not V.D. as in other tissues)

CHAPTER 16

EFFECTS OF EXERCISE ON THE CIRCULATION

An adequate O_2 supply is essential for performance of muscular exercise. The resting O_2 consumption (250 ml / minute) may increase 20 times or more during exercise. The circulatory adjustments during exercise aim at increasing the muscular blood flow. This may increase 30-fold as a result of both *systemic circulatory changes and local changes in the active muscles*.

(A) SYSTEMIC CIRCULATORY CHANGES

(1) Increase of the cardiac output (CO)

The CO increases due to an increase in the heart rate and stroke volume.

(a) The heart rate : This increases up to 180-200 beats/minute as a result of

(1) Psychic stimuli from the cerebral cortex (which stimulate the VCC)

(2) Bainbridge reflex (which is initiated by the increased venous return).

(3) Alam smirk reflex (which is initiated by muscle contraction).

(4) The increase in PCO_2 and H^+ (which activate the VCC through stimulating the central and peripheral chemoreceptors).

(5) Rise of the blood temperature (which stimulates the S-A node).

(b) The stroke volume : This increases due to forceful ventricular contraction produced by the increased symp. activity and catecholamines secretion.

(2) Increase of the venous return

This is increased as a result of: **(a)** An increase in both the muscle and respiratory pumps **(b)** Mobilization of blood from the viscera and other reservoirs (see below). **(c)** Arteriolar dilatation in the active muscles **(d)** Venoconstriction produced by the increased sympathetic activity.

(3) Increase of the arterial blood pressure

The increased CO elevates the mean arterial pressure. The systolic pressure increases markedly due to the increase in the stroke volume, while the diastolic pressure is unchanged or even falls slightly because the total peripheral resistance decreases as a result of the marked V.D. in the active muscles.

(4) Generalized V.C. (redistribution of blood)

Generalized V.C. occurs in areas other than the active muscles, specially *the splanchnic area and skin*, so blood is shifted to the active muscles and the heart (where V.D. occurs). This V.C. is produced by the increased sympathetic activity which occurs as a result of stimulation of the VCC by the psychic stimuli and the raised PCO_2 and H^+ (see above)

****** If the exercise is prolonged and the body temperature increases, the cutaneous V.D. occurs to increase the rate of heat loss. Also the prolonged V.C of the renal vessels may result in transient *albuminuria*.

(B) LOCAL CHANGES IN THE ACTIVE MUSCLES

(1) V.D. of the muscle arterioles

This together with the above systemic effects, leads to a marked increase in the muscle blood flow. It occurs even before starting the exercise through activation of the **sympathetic V.D. system** (refer to the autonomic N.S.) and is then maintained and augmented by the effects of :

- a- The V.D. metabolites e.g. (K^+ and adenosine).
- b- The local O_2 lack and increased PCO_2 and H^+ (lactic acid).
- c- The excess heat liberated in the active muscles.
- d- The increased arterial B.P. (which mechanically dilates the arterioles).

(2) Capillary changes

The precapillary sphincters are relaxed, so the open capillaries increase 10-100 times, and they become widely dilated. These effects increase the capillary pressure and permeability, which favours filtration of more fluid that contains the nutrients required for muscle contraction.

(3) Increase of the lymph flow

Large amounts of lymph are formed in active muscles due to the excessive filtration of the interstitial fluid (see above). This is associated with increased lymph flow from the active muscles as a result of the increase of their pumping power (which also increases the venous return). This effect helps to decrease the local edema that may occur in active muscles

(4) Increase of the oxygen uptake

In active muscles, the O_2 consumption increases markedly as a result of the following effects :

- (a) The marked increase in the muscle blood flow rate (see above).
- (b) More unloading of O_2 from oxyHb : This is helped by the local increase in CO_2 , H^+ and temperature, as well as by the increase in 2,3 DPG (= 2, 3 diphosphoglycerate) in the red cells. All these factors decrease the O_2 affinity to Hb, and *shift the O_2 dissociation curve to the right*, and at the same time facilitates CO_2 carriage from active muscles by the formed reduced Hb through the Haldane's effect (refer to respiration).
- (c) The slow blood flow (due to V.D.), which increases O_2 extraction.

CHAPTER 17

HEMORRHAGE, SHOCK AND HEART FAILURE

Hemorrhage means loss of blood from the CVS, and it is 2 types :

- (1) **Chronic** : This is loss of small amounts of blood over a long period in a repeated manner (e.g. as a result of an infection with ankylostoma or bilharzia worms). It is not fatal, and it only leads to **hemorrhagic anemia**.
- (2) **Acute** : This is *sudden loss of a large volume of blood*. Mild and moderate cases can be compensated, but severe cases (loss of more than 30 % of the blood volume) are usually **fatal** (unless early and properly treated) as a result of the **hypotension** that occurs secondary to **hypovolemia**.

COMPENSATORY REACTIONS IN ACUTE HEMORRHAGE

(I) Immediate (short-term or rapid) reactions

These aim at rapid elevation of the arterial B.P. by producing V.C. and increasing the cardiac output and blood volume. They include the following :

- (1) **Excitation of the VCC** : This occurs within *30 seconds to one minute* as a result of (a) *Its release from the inhibitory effect of the arterial baroreceptors* (b) *Its stimulation by impulses discharged from the chemoreceptors under effect of O₂ lack* (c) *The CNS ischemic response*, which acts only when the arterial blood pressure drops below 50 or 60 mmHg (page 105).

Excitation of the VCC leads to **activation of the sympathetic N.S. and secretion of catecholamines from the adrenal medullae** and both help elevation of the arterial blood pressure through producing the following effects:

- (a) Increase of the stroke volume and heart rate (which increases the cardiac output).
- (b) Generalized **arteriolar V.C.** specially in the skin and viscera (but not in the heart and brain) which increases the peripheral resistance.
- (c) Generalized **venoconstriction**, which increases the mean circulatory pressure and the venous return, thus increasing the cardiac output.
- (d) Contraction of the splenic capsule, which shifts the stored concentrated blood in the spleen (normally about 50 ml) into the general circulation
- (2) **Reverse stress relaxation**, which also leads to V.C. (page 105).
- (3) **Activation of the renin-angiotensin system** : Renal ischemia and the increased sympathetic activity lead to secretion of **renin** and formation of **angiotensin II** which causes V.C. and stimulates secretion of both **aldosterone** (promotes renal Na⁺ absorption) and **ADH (= vasopressin)** which causes water retention in the body and also a potent V.C. effect.

(4) **Fluid shift** : The decrease of capillary pressure enhances fluid absorption from the interstitial (tissue) spaces into the bloodstream (= *auto-transfusion*). Fluids are also absorbed from the intestinal tract.

(5) **Mobilization of preformed protein** (the labile reserve tissue proteins) into the bloodstream.

(II) Delayed (long term or slow) reactions

These aim at restoration of the blood volume and the various blood elements in order to keep a normal arterial B.P. They include the following :

(1) **Restoration of the plasma volume** : This occurs in 12 – 72 hours as a result of :

(a) Secretion of **aldosterone and ADH** (under effect of *angiotensin II*) which promote Na^+ and water retention in the body (see above). ADH is also released as a result of decreased pressure in both the right atrium as well as the carotid sinus and aortic arch (page 73)

(b) **Increased thirst sensation and salt appetite** (which increases both water and salt intake) as a result of stimulation of the thirst and salt appetite centres in the anterior hypothalamus under effect of angiotensin II as well as secondary to decreased pressure in the right atrium (refer to kidney).

(c) **Increased Na^+ retention by the kidneys** as a result of deficient renal excretion (due to decreased renal blood flow and glomerular filtration secondary to hypovolemia and V.C. of the renal arterioles) as well as by the effects of **aldosterone and angiotensin II** (page 108)

(2) **Restoration of the plasma proteins** : The plasma proteins are restored within 3 – 4 days through increased synthesis by the liver from the reserve tissue proteins as well as the proteins supplied in the diet.

(3) **Restoration of the red blood cells** : The red blood cell count is restored within 4 – 8 weeks through increased formation in the bone marrow by effect of the **erythropoietin hormone** (which is secreted by the kidneys in response to O_2 lack).

**** The hormones involved in the compensatory reactions in cases of acute hemorrhage include the following :**

(1) Catecholamines (from the adrenal medullae).

(2) ADH (= vasopressin) from the posterior pituitary gland.

(3) Aldosterone (from the adrenal cortex).

(4) Erythropoietin (from the kidneys as a result of hypoxia).

(5) ACTH (Adreno-Cortico-Tropic Hormone) : This is secreted from the anterior pituitary gland *in stress conditions and also in response to angiotensin II*. It stimulates release of glucocorticoids from the adrenal cortex, which increase the V.C. effect of catecholamines and also cause Na^+ retention like aldosterone but to a smaller extent (refer to endocrine glands).

SIGNS & SYMPTOMS (MANIFESTATIONS) OF ACUTE HEMORRHAGE

- (1) **Hypotension**. (decrease of both the mean and pulse pressures).
- (2) Rapid weak pulse (**thready pulse**, page 41) due to tachycardia (induced by sympathetic activity) associated with decrease of the stroke volume.
- (3) Rapid respiration (**tachypnea**) : This is due to stimulation of the respiratory centre as a result of the *increased PCO₂ and decreased PO₂* (through stimulating the central and peripheral chemoreceptors respectively).
- (4) Thirst sensation and increased desire for water (see above).
- (5) Pale and cold skin (due to cutaneous V.C.).
- (6) Excessive sweating (due to the increased sympathetic activity).
- (7) Oliguria (due to V.C. of the renal vessels and water retention by ADH).
- (8) Anxiety and restlessness (due to reticular formation excitation by catecholamines) or quietness and apathy (due to cerebral ischemia and acidosis).

CIRCULATORY SHOCK

This is a clinical syndrome characterized by **tissue hypoperfusion with blood due to decrease in the cardiac output and arterial blood pressure**. It occurs as a result of either blood loss (= **hypovolemic shock**) or other conditions in which *the blood volume is normal* (= **normovolemic shock**). The latter include the **cardiogenic, obstructive and distributive shock**.

THE HYPOVOLEMIC SHOCK (= COLD SHOCK)

This occurs as a result of reduction of the blood volume. Its manifestations are those of acute hemorrhage (see above). Its main causes include (1) Acute hemorrhage (**hemorrhagic shock**) (2) Severe trauma (**traumatic shock**) (3) Major surgery (**surgical shock**) (4) Loss of large amounts of plasma e.g. from extensive burns (**burn shock**) (5) **Dehydration** (e.g. as a result of severe diarrhea, vomiting or sweating). Because the skin is pale and cold in this type of shock (due to V.C.), it is also referred to as "**cold shock**".

THE CARDIOGENIC (= CONGESTED) and OBSTRUCTIVE SHOCK

These occur as a result of inadequate pumping action of the heart which leads to reduction of the cardiac output and arterial blood pressure. The main causes of **cardiogenic shock** include (1) Extensive left ventricular infarction (2) Acute myocarditis (3) Heart failure. (4) Certain ventricular arrhythmias.. Because there is congestion in the lungs and viscera in this condition, it is also referred to as "**congested shock**". Cases that limit cardiac filling (e.g. a massive pericardial effusion or a large pneumothorax) decrease the cardiac output and may also lead to shock that is called **obstructive shock**.

DISTRIBUTIVE (= LOW RESISTANCE, VASOGENIC or WARM) SHOCK

This type of shock is due to *widespread arteriolar V.D. and venodilatation* (while the blood volume is normal), which lead to acute drop of the venous return, cardiac output and arterial blood pressure, resulting in tissue hypoperfusion. It includes the following types :

(1) Neurogenic shock : This occurs in severe emotions (e.g. fear and grief) as well as in cases associated with severe pain e.g. severe trauma and burns (so *traumatic and burn shock have both hypovolemic and neurogenic features*). In these cases, signals from certain areas in the cerebral cortex inhibit the normal sympathetic V.C. tone, resulting in *generalized V.D.* This leads to shock, and fainting also often occurs (a condition called **vaso-vagal attack**)

(2) Septic shock : This occurs in *certain bacterial infections*. It has both distributive and hypovolemic features because the **endotoxin** released from the bacteria causes V.D. (which also occurs by effect of fever) and increased capillary permeability with loss of plasma in the tissues. The endotoxin also causes red cell agglutination & intravascular coagulation. This leads to multiple organ failure and *cardiac depression*, which makes shock more worse

(3) Anaphylactic (allergic) shock : This occurs in *severe allergic conditions* due to widespread V.D. that is produced as a result of release of *histamine* during antigen-antibody reactions (= **histamine shock**).

****** Cases of *distributive shock* are sometimes called **warm shock** because the skin temperature in these cases is **not cold** due to V.D. Also, because of V.D., these conditions are called **low resistance shock**.

TYPES (STAGES) OF HEMORRHAGIC SHOCK

(1) Reversible (nonprogressive or compensated shock) : This occurs in mild cases of hemorrhage, in which the body compensatory mechanisms (page 143) are capable to restore the normal blood volume and arterial blood pressure *even without help from outside therapy*.

(2) Progressive shock : This occurs in moderate cases of hemorrhage in which, *without external therapy*, shock progresses within a few hours to the next stage. However, *with proper treatment, the condition is still reversible*.

(3) Irreversible (uncompensated or refractory shock) : This occurs in severe hemorrhage. In such cases, there will be *no response to vasopressor drugs or any other lines of treatment* and death eventually occurs *even if the blood volume was restored* (see next).

Mechanism of progressive and irreversible shock (+ve feedbacks and vicious circles of circulatory deterioration)

In cases of shock, there is a critical cardiac output above which shock recovers (in compensated shock) and below which shock persists. In the progressive stage, shock **progresses as a result of several +ve feed-back mechanisms** (see below). In mild and moderate cases of shock, these mechanisms can be blocked by proper treatment and the patient is saved. However, in severe cases these mechanisms are often so strong that they develop into **vicious circles of circulatory deterioration** which leads to the irreversible stage of shock that eventually terminates by death

Some of the +ve feed-back mechanisms and the vicious circles of circulatory deterioration proceed as follows :

(1) Hypotension → cerebral ischemia → depression of the VCC and the cardiac centres → V.D. and bradycardia → more hypotension (and the events are repeated by a +ve feedback mechanism).

(2) Hypotension → decrease of coronary blood flow → cardiac depression → decrease of the cardiac output → more hypotension (and the events are repeated by a +ve feedback mechanism).

****** There are other factors that cause cardiac depression and enhance development of irreversible shock e.g. (1) Acidosis that occurs due to excessive formation of lactic acid as a result of anaerobic glycolysis (2) Electrolyte disturbances that occur as a result of impairment of renal function due to ischemia (3) Increased capillary permeability (due to O₂ lack) which leads to fluid loss in the tissues and decreases the blood volume (4) Blood clotting in microvessels due to the sluggish blood flow.

HEART FAILURE (HF)

Definition : HF is the inability of the heart to pump an adequate output for the normal body metabolic needs. This may be the result of either a defect in systole (**systolic HF**) or in diastole (**diastolic HF**) or both (the commonest).

Grades : HF may be **mild** (signs of HF appear only during activity) or **severe** (signs of HF appear during rest). It may also be **acute** or **chronic**.

Causes : HF may occur as a result of either (1) **Heart disease** e.g. coronary insufficiency, valvular diseases, myocarditis or myocardial depression by certain toxins (2) **Increased afterload** (e.g. due to hypertension) or **preload** (e.g. due to hyperthyroidism) (3) **Massive pericardial effusion** (which causes heart compression that leads to *secondary heart failure*).

Low output and high output failure

Most cases of HF are associated with a low cardiac output. However, in some cases (e.g. anemia and hyperthyroidism) there is **volume overload** and HF may occur although the heart pumps *a greater output than normal*. Thus, such condition is called a **high output failure** and is characterized by warm skin and a high pulse pressure (*water hammer pulse*, page 41)..

LEFT SIDED HF(left ventricular failure)

The commonest causes of left ventricular failure are *coronary artery disease, chronic arterial hypertension and certain valvular diseases* e.g. aortic stenosis and incompetence. Its main manifestations are (1) Left ventricular dilatation (2) Gallop rhythm (page 37) (3) Pulsus alternans (page 40) (4) **Signs of forward failure** : These are the result of the decreased cardiac output. They include muscle weakness and rapid fatigue (due to muscle hypoperfusion), cold extremities, skin pallor and peripheral cyanosis.

(5) **Signs of backward failure** : These are the result of *pulmonary congestion* (increase of the pulmonary venous & capillary pressures) and include :

(a) **Dyspnea** : This first occurs on exertion, but later it becomes continuous. It may occur only in the recumbent position (= **orthopnea**) or as severe night attacks (**cardiac asthma**).

(b) **Cough** (due to irritation of the congested bronchial mucosa).

(c) **Pulmonary edema** (may be fatal in acute cases) : This occurs due to rise of the pulmonary capillary hydrostatic pressure (page 139).

(d) **Pulmonary hypertension** (139).

RIGHT SIDED HF (right ventricular failure)

Right ventricular failure may occur *on top of left-sided heart failure* (due to loss of left ventricular aid) or secondary to pulmonary hypertension e.g. due to mitral stenosis or lung diseases that cause **cor pulmonale** (page 139). It also occurs in cases of pulmonary valve stenosis, but it is *rarely due to coronary insufficiency*. Its main manifestations are the following :

(1) Right ventricular dilatation.

(2) **Signs of forward failure** (the same as those caused by left ventricular failure because the cardiac output is also decreased in this case).

(3) **Signs of backward failure** : These are the result of *systemic congestion* (increase of CVP and peripheral venous & capillary pressures) and include :

(a) **Systemic (body) edema**: This initially occurs in the dependent parts of the body (as a result of the force of gravity), so it is first noted in the ankles, but after prolonged recumbency it appears in the sacral region. Excess filtration of fluid in the peritoneum may also occur leading to **ascites**.

(b) Enlargement of the liver (hepatomegaly).

(c) Congested (distended) neck veins.

Physiological compensatory responses to HF

(A) Cardiac responses

- (1) **Increase of EDV** (due to low CO) : This allows use of the Starling law to increase the stroke volume by heterometric autoregulation.
- (2) **Increase of cardiac contractility** (by homeometric autoregulation).
- (3) **Cardiac hypertrophy** (increases the cardiac contractile power).

(B) Neuro-hormonal responses

- (1) **Stimulation of the sympathetic N.S.** (through the arterial baroreflex) helps increasing the cardiac output and arterial B.P. by (a) Increasing the cardiac contractility and heart rate (b) Producing arteriolar V.C. (increases the peripheral resistance) and venoconstriction (increases the venous return).
- (2) **Renal responses** : The renal underperfusion (due to the decreased cardiac output) results in activation of the *renin-angiotensin system*. Angiotensin II causes V.C. and Na^+ and water retention in the body (page 108) which increases the EDV, thus the cardiac contractility and output are increased.
- (3) The *atrial natriuretic peptide* (ANP) is secreted in cases of HF (as a result of stretch of the atrial walls). It *prevents excessive salt and water retention in the body, which is important in chronic cases of HF* (see next).

Exhaustion of the compensatory mechanisms (HF progression)

Without proper treatment, the compensatory mechanisms to HF will be gradually exhausted (= **decompensation**) as a result of the following :

- (1) With prolonged sympathetic overactivity, its +ve inotropic and chronotropic effects will be gradually decreased and the heart will depend only on the Frank-Starling mechanism for its performance.
- (2) The Frank-Starling mechanism also has a limit beyond which it fails.
- (3) Cardiac hypertrophy also has a limit, beyond which the ability of the hypertrophied muscle to generate force is decreased (page 91).
- (4) The prolonged V.C. produced by sympathetic overactivity and angiotensin II increases the cardiac afterload (by increasing the peripheral resistance), and this decreases the cardiac contractility.
- (5) When the cardiac output is decreased as a result of exhaustion of the cardiac reserve mechanisms, the excess salt and water retention becomes a disadvantage, and its persistence represents an overload to the heart.

PHYSIOLOGICAL BASIS OF TREATMENT OF HEART FAILURE

Management of HF aims at decreasing the cardiac work and improving the power of cardiac contractility. This can be achieved as follows :

(A) General measures

- (1) **Rest** (to decrease the cardiac work).
- (2) **Low-salt diet** (to decrease fluid retention in the body, thus preventing excessive increase of blood volume which decreases the cardiac work).

(B) Use of drugs

- (1) **Cardiac glycosides (e.g. digitalis)** : These drugs exert a + ve inotropic action, so they improve the power of cardiac contractility, page 26).
- (2) **Vasodilator drugs** (help reduction of the cardiac afterload)
- (3) **Diuretics** (enhance salt and water excretion, thus helping reduction of the blood volume, which decreases the cardiac work).
- (4) **ACE inhibitors** (page 110) : These drugs inhibit formation of angiotensin II. This decreases both V.C. as well as aldosterone secretion, thus the peripheral resistance and salt and water retention are decreased leading to reduction of the cardiac work

FAINTING (SYNCOPE)

This is sudden transient loss of consciousness (fainting) due to cerebral ischemia. Some of the causes of syncope include the following :

(1) **Vasovagal syncope** : This occurs in some individuals exposed to a severe emotion. Cortical impulses depress the VCC and stimulate the CIC leading to bradycardia and widespread V.D. (specially in skeletal muscles because the sympathetic V.D. system is also activated). These effects result in hypotension which leads to cerebral ischemia and syncope (page 110).

(2) **Orthostatic syncope** (due to postural hypotension, page 127).

(3) **Carotid sinus syncope** (due to hypersensitivity of the baroreceptors in the carotid sinus, page 73).

(4) **Cardiogenic syncope** (syncope due to heart block or sinus arrest). Syncope may also occur as a result of myocardial infarction, in certain arrhythmias and in the Stokes-Adams syndrome (page 67).

(5) **Effort syncope** (this is common in patients having aortic or pulmonary stenosis).

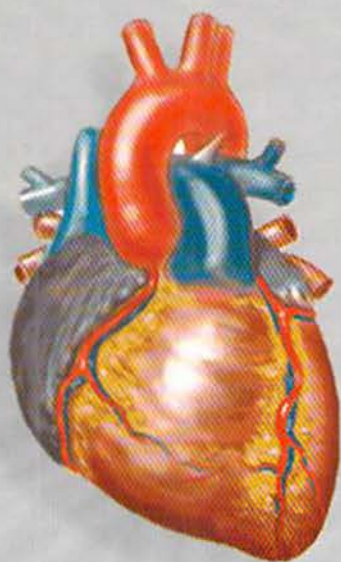
(6) **Micturition syncope (in men only)** : This may occur in some individuals due to orthostatic hypotension and reflex bradycardia induced by voiding urine.

(7) **Cough syncope** (due to decrease of the venous return as a result of rise of the intrathoracic pressure, which reduces the cardiac output leading to hypotension and syncope).

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